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(54) Title: COMPOSITIONS, SPLICE VARIANTS AND METHODS RELATING TO BREAST SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acid molecules and polypeptides present in normal and neoplastic breast cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions containing the nucleic acid molecules, polypeptides, antibodies, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast, identifying breast tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered breast tissue for treatment and research.

**COMPOSITIONS, SPLICE VARIANTS AND METHODS
RELATING TO BREAST SPECIFIC GENES AND PROTEINS**

5

INTRODUCTION

This application claims the benefit of priority from U.S. Provisional Patent Application Serial No. 60/431,097 filed December 5, 2002 and 60/431,122 filed December 5, 2002 which are herein incorporated by reference in their entireties.

FIELD OF THE INVENTION

10 The present invention relates to newly identified nucleic acids and polypeptides present in normal and neoplastic breast cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions comprising the nucleic acids, 15 polypeptides, antibodies, post translational modifications (PTMs), variants, derivatives, agonists and antagonists thereto and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast, identifying breast tissue and monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. 20 The uses also include gene therapy, therapeutic molecules including but not limited to antibodies or antisense molecules, production of transgenic animals and cells, and production of engineered breast tissue for treatment and research.

BACKGROUND OF THE INVENTION

25 Breast cancer, also referred to as mammary tumor cancer, is the second most common cancer among women, accounting for a third of the cancers diagnosed in the United States. One in nine women will develop breast cancer in her lifetime and about 192,000 new cases of breast cancer are diagnosed annually with about 42,000 deaths. Bevers, *Primary Prevention of Breast Cancer*, in *Breast Cancer*, 20-54 (Kelly K Hunt et al., ed., 2001); Kochanek *et al.*, 49 *Nat'l. Vital Statistics Reports* 1, 14 (2001). Breast 30 cancer is extremely rare in women younger than 20 and is very rare in women under 30. The incidence of breast cancer rises with age and becomes significant by age 50. White Non-Hispanic women have the highest incidence rate for breast cancer and Korean women have the lowest. Increased prevalence of the genetic mutations BRCA1 and BRCA2 that

promote breast and other cancers are found in Ashkenazi Jews. African American women have the highest mortality rate for breast cancer among these same groups (31 per 100,000), while Chinese women have the lowest at 11 per 100,000. Although men can get breast cancer, this is extremely rare. In the United States it is estimated there will be

- 5 212,600 new cases of breast cancer and 40,200 deaths due to breast cancer in 2003. (American Cancer Society Website: cancer.org at the world wide web). With the exception of those cases with associated genetic factors, precise causes of breast cancer are not known.

In the treatment of breast cancer, there is considerable emphasis on detection and
10 risk assessment because early and accurate staging of breast cancer has a significant impact on survival. For example, breast cancer detected at an early stage (stage T0, discussed below) has a five-year survival rate of 92%. Conversely, if the cancer is not detected until a late stage (i.e., stage T4 (IV)), the five-year survival rate is reduced to 13%. AJCC Cancer Staging Handbook pp. 164-65 (Irvin D. Fleming *et al.* eds., 5th ed.
15 1998). Some detection techniques, such as mammography and biopsy, involve increased discomfort, expense, and/or radiation, and are prescribed only to patients with an increased risk of breast cancer.

Current methods for predicting or detecting breast cancer risk are not optimal. One method for predicting the relative risk of breast cancer is by examining a patient's risk factors and pursuing aggressive diagnostic and treatment regimens for high risk patients.
20 A patient's risk of breast cancer has been positively associated with increasing age, nulliparity, family history of breast cancer, personal history of breast cancer, early menarche, late menopause, late age of first full term pregnancy, prior proliferative breast disease, irradiation of the breast at an early age and a personal history of malignancy.
25 Lifestyle factors such as fat consumption, alcohol consumption, education, and socioeconomic status have also been associated with an increased incidence of breast cancer although a direct cause and effect relationship has not been established. While these risk factors are statistically significant, their weak association with breast cancer limits their usefulness. Most women who develop breast cancer have none of the risk
30 factors listed above, other than the risk that comes with growing older. NIH Publication No. 00-1556 (2000).

Current screening methods for detecting cancer, such as breast self exam, ultrasound, and mammography have drawbacks that reduce their effectiveness or prevent

their widespread adoption. Breast self exams, while useful, are unreliable for the detection of breast cancer in the initial stages where the tumor is small and difficult to detect by palpation. Ultrasound measurements require skilled operators at an increased expense. Mammography, while sensitive, is subject to over diagnosis in the detection of lesions that 5 have questionable malignant potential. There is also the fear of the radiation used in mammography because prior chest radiation is a factor associated with an increased incidence of breast cancer.

At this time, there are no adequate methods of breast cancer prevention. The current methods of breast cancer prevention involve prophylactic mastectomy 10 (mastectomy performed before cancer diagnosis) and chemoprevention (chemotherapy before cancer diagnosis) which are drastic measures that limit their adoption even among women with increased risk of breast cancer. Bevers, *supra*.

A number of genetic markers have been associated with breast cancer. Examples of these markers include carcinoembryonic antigen (CEA) (Mughal *et al.*, *JAMA* 249:1881 15 (1983)), MUC-1 (Frische and Liu, *J. Clin. Ligand* 22:320 (2000)), HER-2/neu (Haris *et al.*, *Proc.Am.Soc.Clin.Oncology* 15:A96 (1996)), uPA, PAI-1, LPA, LPC, RAK and BRCA (Esteva and Fritzsche, *Serum and Tissue Markers for Breast Cancer*, in Breast Cancer, 286-308 (2001)). These markers have problems with limited sensitivity, low correlation, and false negatives which limit their use for initial diagnosis. For example, 20 while the BRCA1 gene mutation is useful as an indicator of an increased risk for breast cancer, it has limited use in cancer diagnosis because only 6.2 % of breast cancers are BRCA1 positive. Malone *et al.*, *JAMA* 279:922 (1998). See also, Mewman *et al.*, *JAMA* 279:915 (1998) (correlation of only 3.3%).

There are four primary classifications of breast cancer varying by the site of origin 25 and the extent of disease development.

- I. Ductal carcinoma in situ (DCIS): Malignant transformation of ductal epithelial cells that remain in their normal position. DCIS is a purely localized disease, incapable of metastasis.
- II. Invasive ductal carcinoma (IDC): Malignancy of the ductal epithelial cells breaking through the basal membrane and into the supporting tissue of the breast. IDC may eventually spread elsewhere in the body.
- III. Lobular carcinoma in situ (LCIS): Malignancy arising in a single lobule of the breast that fail to extend through the lobule wall, it generally remains localized.

IV. Infiltrating lobular carcinoma (ILC): Malignancy arising in a single lobule of the breast and invading directly through the lobule wall into adjacent tissues.

By virtue of its invasion beyond the lobule wall, ILC may penetrate lymphatics and blood vessels and spread to distant sites.

5 For purpose of determining prognosis and treatment, these four breast cancer types have been staged according to the size of the primary tumor (T), the involvement of lymph nodes (N), and the presence of metastasis (M). Although DCIS by definition represents localized stage I disease, the other forms of breast cancer may range from stage II to stage IV. There are additional prognostic factors that further serve to guide surgical and medical 10 intervention. The most common ones are total number of lymph nodes involved, ER (estrogen receptor) status, Her2/neu receptor status and histologic grades.

Breast cancers are diagnosed into the appropriate stage categories recognizing that different treatments are more effective for different stages of cancer. Stage TX indicates that primary tumor cannot be assessed (i.e., tumor was removed or breast tissue was 15 removed). Stage T0 is characterized by abnormalities such as hyperplasia but with no evidence of primary tumor. Stage Tis is characterized by carcinoma in situ, intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor. Stage T1 (I) is characterized as having a tumor of 2 cm or less in the greatest dimension. Within stage T1, Tmic indicates microinvasion of 0.1 cm or less, T1a indicates a tumor of 20 between 0.1 to 0.5 cm, T1b indicates a tumor of between 0.5 to 1 cm, and T1c indicates tumors of between 1 cm to 2 cm. Stage T2 (II) is characterized by tumors from 2 cm to 5 cm in the greatest dimension. Tumors greater than 5 cm in size are classified as stage T3 (III). Stage T4 (IV) indicates a tumor of any size with extension to the chest wall or skin. Within stage T4, T4a indicates extension of the tumor to the chest wall, T4b indicates 25 edema or ulceration of the skin of the breast or satellite skin nodules confined to the same breast, T4c indicates a combination of T4a and T4b, and T4d indicates inflammatory carcinoma. AJCC Cancer Staging Handbook pp. 159-70 (Irvin D. Fleming *et al.* eds., 5th ed. 1998). In addition to standard staging, breast tumors may be classified according to their estrogen receptor and progesterone receptor protein status. Fisher *et al.*, *Breast 30 Cancer Research and Treatment* 7:147 (1986). Additional pathological status, such as HER2/neu status may also be useful. Thor *et al.*, *J.Nat'l.Cancer Inst.* 90:1346 (1998); Paik *et al.*, *J.Nat'l.Cancer Inst.* 90:1361 (1998); Hutchins *et al.*,

Proc.Am.Soc.Clin.Oncology 17:A2 (1998).; and Simpson *et al.*, *J.Clin.Oncology* 18:2059 (2000).

In addition to the staging of the primary tumor, breast cancer metastases to regional lymph nodes may be staged. Stage NX indicates that the lymph nodes cannot be assessed (e.g., previously removed). Stage N0 indicates no regional lymph node metastasis. Stage N1 indicates metastasis to movable ipsilateral axillary lymph nodes. Stage N2 indicates metastasis to ipsilateral axillary lymph nodes fixed to one another or to other structures. Stage N3 indicates metastasis to ipsilateral internal mammary lymph nodes. *Id.*

Stage determination has potential prognostic value and provides criteria for designing optimal therapy. Simpson *et al.*, *J. Clin. Oncology* 18:2059 (2000). Generally, pathological staging of breast cancer is preferable to clinical staging because the former gives a more accurate prognosis. However, clinical staging would be preferred if it were as accurate as pathological staging because it does not depend on an invasive procedure to obtain tissue for pathological evaluation. Staging of breast cancer would be improved by detecting new markers in cells, tissues, or bodily fluids which could differentiate between different stages of invasion. Progress in this field will allow more rapid and reliable method for treating breast cancer patients.

Treatment of breast cancer is generally decided after an accurate staging of the primary tumor. Primary treatment options include breast conserving therapy (lumpectomy, breast irradiation, and surgical staging of the axilla), and modified radical mastectomy. Additional treatments include chemotherapy, regional irradiation, and, in extreme cases, terminating estrogen production by ovarian ablation.

Until recently, the customary treatment for all breast cancer was mastectomy. Fonseca *et al.*, *Annals of Internal Medicine* 127:1013 (1997). However, recent data indicate that less radical procedures may be equally effective, in terms of survival, for early stage breast cancer. Fisher *et al.*, *J. of Clinical Oncology* 16:441 (1998). The treatment options for a patient with early stage breast cancer (i.e., stage Tis) may be breast-sparing surgery followed by localized radiation therapy at the breast. Alternatively, mastectomy optionally coupled with radiation or breast reconstruction may be employed. These treatment methods are equally effective in the early stages of breast cancer.

Patients with stage I and stage II breast cancer require surgery with chemotherapy and/or hormonal therapy. Surgery is of limited use in stage III and stage IV patients.

Thus, these patients are better candidates for chemotherapy and radiation therapy with surgery limited to biopsy to permit initial staging or subsequent restaging because cancer is rarely curative at this stage of the disease. AJCC Cancer Staging Handbook 84, 164-65 (Irvin D. Fleming *et al.* eds., 5th ed.1998).

- 5 In an effort to provide more treatment options to patients, efforts are underway to define an earlier stage of breast cancer with low recurrence which could be treated with lumpectomy without postoperative radiation treatment. While a number of attempts have been made to classify early stage breast cancer, no consensus recommendation on postoperative radiation treatment has been obtained from these studies. Page *et al.*,
10 *Cancer* 75:1219 (1995); Fisher *et al.*, *Cancer* 75:1223 (1995); Silverstein *et al.*, *Cancer* 77:2267 (1996).

Cancer of the ovaries is the fourth most common cause of cancer death in women in the United States, with more than 23,000 new cases and roughly 14,000 deaths predicted for the year 2001. Shridhar, V. *et al.*, *Cancer Res.* 61(15):5895-904 (2001);
15 Memarzadeh, S. & Berek, J. S., *J. Reprod. Med.* 46(7):621-29 (2001). The incidence of ovarian cancer is of serious concern worldwide, with an estimated 191,000 new cases predicted annually. Runnebaum, I. B. & Stickeler, E., *J.Cancer Res. Clin. Oncol.* 127(2):73-79 (2001). These numbers continue to rise today. In the United States alone, it is estimated there will be 25,400 new cases of ovarian cancer, and 14,300 deaths
20 due to ovarian cancer in 2003. (American Cancer Society Website: <http://www.cancer.org>). Unfortunately, women with ovarian cancer are typically asymptomatic until the disease has metastasized. Because effective screening for ovarian cancer is not available, roughly 70% of women diagnosed have an advanced stage of the cancer with a five-year survival rate of ~25-30%. Memarzadeh, S. & Berek, J. S., *supra*;
25 Nunns, D. *et al.*, *Obstet. Gynecol. Surv.* 55(12):746-51. Conversely, women diagnosed with early stage ovarian cancer enjoy considerably higher survival rates. Werness, B. A. & Eltabbakh, G. H., *Int'l. J. Gynecol. Pathol.* 20(1):48-63 (2001). Although our understanding of the etiology of ovarian cancer is incomplete, the results of extensive research in this area point to a combination of age, genetics, reproductive, and
30 dietary/environmental factors. Age is a key risk factor in the development of ovarian cancer: while the risk for developing ovarian cancer before the age of 30 is slim, the incidence of ovarian cancer rises linearly between ages 30 to 50, increasing at a slower rate thereafter, with the highest incidence being among septagenarian women. Jeanne M.

Schilder *et al.*, *Heredity Ovarian Cancer: Clinical Syndromes and Management*, in *Ovarian Cancer* 182 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001).

With respect to genetic factors, a family history of ovarian cancer is the most significant risk factor in the development of the disease, with that risk depending on the
5 number of affected family members, the degree of their relationship to the woman, and which particular first degree relatives are affected by the disease. *Id.* Mutations in several genes have been associated with ovarian cancer, including BRCA1 and BRCA2, both of which play a key role in the development of breast cancer, as well as hMSH2 and hMLH1, both of which are associated with hereditary non-polyposis colon cancer. Katherine Y.
10 Look, *Epidemiology, Etiology, and Screening of Ovarian Cancer*, in *Ovarian Cancer* 169, 171-73 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001). BRCA1, located on chromosome 17, and BRCA2, located on chromosome 13, are tumor suppressor genes implicated in DNA repair; mutations in these genes are linked to roughly 10% of ovarian cancers. *Id.* at 171-72; Schilder *et al.*, *supra* at 185-86. hMSH2 and hMLH1 are
15 associated with DNA mismatch repair, and are located on chromosomes 2 and 3, respectively; it has been reported that roughly 3% of hereditary ovarian carcinomas are due to mutations in these genes. Look, *supra* at 173; Schilder *et al.*, *supra* at 184, 188-89.

Reproductive factors have also been associated with an increased or reduced risk of ovarian cancer. Late menopause, nulliparity, and early age at menarche have all been
20 linked with an elevated risk of ovarian cancer. Schilder *et al.*, *supra* at 182. One theory hypothesizes that these factors increase the number of ovulatory cycles over the course of a woman's life, leading to "incessant ovulation," which is thought to be the primary cause of mutations to the ovarian epithelium. *Id.*; Laura J. Havrilesky & Andrew Berchuck, *Molecular Alterations in Sporadic Ovarian Cancer*, in *Ovarian Cancer* 25 (Stephen C.
25 Rubin & Gregory P. Sutton eds., 2d ed. 2001). The mutations may be explained by the fact that ovulation results in the destruction and repair of that epithelium, necessitating increased cell division, thereby increasing the possibility that an undetected mutation will occur. *Id.* Support for this theory may be found in the fact that pregnancy, lactation, and the use of oral contraceptives, all of which suppress ovulation, confer a protective effect
30 with respect to developing ovarian cancer. *Id.*

Among dietary/environmental factors, there would appear to be an association between high intake of animal fat or red meat and ovarian cancer, while the antioxidant Vitamin A, which prevents free radical formation and also assists in maintaining normal

cellular differentiation, may offer a protective effect. Look, *supra* at 169. Reports have also associated asbestos and hydrous magnesium trisilicate (talc), the latter of which may be present in diaphragms and sanitary napkins. *Id.* at 169-70.

Current screening procedures for ovarian cancer, while of some utility, are quite limited in their diagnostic ability, a problem that is particularly acute at early stages of cancer progression when the disease is typically asymptomatic yet is most readily treatable. Walter J. Burdette, Cancer: Etiology, Diagnosis, and Treatment 166 (1998); Memarzadeh & Berek, *supra*; Runnebaum & Stickeler, *supra*; Werness & Eltabbakh, *supra*. Commonly used screening tests include biannual rectovaginal pelvic examination, 10 radioimmunoassay to detect the CA-125 serum tumor marker, and transvaginal ultrasonography. Burdette, *supra* at 166.

Pelvic examination has failed to yield adequate numbers of early diagnoses, and the other methods are not sufficiently accurate. *Id.* One study reported that only 15% of patients who suffered from ovarian cancer were diagnosed with the disease at the time of 15 their pelvic examination. Look, *supra* at 174. Moreover, the CA-125 test is prone to giving false positives in pre-menopausal women and has been reported to be of low predictive value in post-menopausal women. *Id.* at 174-75. Although transvaginal ultrasonography is now the preferred procedure for screening for ovarian cancer, it is unable to distinguish reliably between benign and malignant tumors, and also cannot 20 locate primary peritoneal malignancies or ovarian cancer if the ovary size is normal. Schilder *et al.*, *supra* at 194-95. While genetic testing for mutations of the BRCA1, BRCA2, hMSH2, and hMLH1 genes is now available, these tests may be too costly for some patients and may also yield false negative or indeterminate results. Schilder *et al.*, *supra* at 191-94.

25 The staging of ovarian cancer, which is accomplished through surgical exploration, is crucial in determining the course of treatment and management of the disease. AJCC Cancer Staging Handbook 187 (Irvin D. Fleming *et al.* eds., 5th ed. 1998); Burdette, *supra* at 170; Memarzadeh & Berek, *supra*; Shridhar *et al.*, *supra*. Staging is performed by reference to the classification system developed by the International Federation of 30 Gynecology and Obstetrics. David H. Moore, *Primary Surgical Management of Early Epithelial Ovarian Carcinoma*, in Ovarian Cancer 203 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001); Fleming *et al.* eds., *supra* at 188. Stage I ovarian cancer is characterized by tumor growth that is limited to the ovaries and is comprised of three

substages. *Id.* In substage IA, tumor growth is limited to one ovary, there is no tumor on the external surface of the ovary, the ovarian capsule is intact, and no malignant cells are present in ascites or peritoneal washings. *Id.* Substage IB is identical to A1, except that tumor growth is limited to both ovaries. *Id.* Substage IC refers to the presence of tumor growth limited to one or both ovaries, and also includes one or more of the following characteristics: capsule rupture, tumor growth on the surface of one or both ovaries, and malignant cells present in ascites or peritoneal washings. *Id.*

Stage II ovarian cancer refers to tumor growth involving one or both ovaries, along with pelvic extension. *Id.* Substage IIA involves extension and/or implants on the uterus and/or fallopian tubes, with no malignant cells in the ascites or peritoneal washings, while substage IIB involves extension into other pelvic organs and tissues, again with no malignant cells in the ascites or peritoneal washings. *Id.* Substage IIIC involves pelvic extension as in IIA or IIB, but with malignant cells in the ascites or peritoneal washings. *Id.*

Stage III ovarian cancer involves tumor growth in one or both ovaries, with peritoneal metastasis beyond the pelvis confirmed by microscope and/or metastasis in the regional lymph nodes. *Id.* Substage IIIA is characterized by microscopic peritoneal metastasis outside the pelvis, with substage IIIB involving macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension. *Id.* Substage IIIC is identical to IIIB, except that the metastasis is greater than 2 cm in greatest dimension and may include regional lymph node metastasis. *Id.* Lastly, Stage IV refers to the presence of distant metastasis, excluding peritoneal metastasis. *Id.*

While surgical staging is currently the benchmark for assessing the management and treatment of ovarian cancer, it suffers from considerable drawbacks, including the invasiveness of the procedure, the potential for complications, as well as the potential for inaccuracy. Moore, *supra* at 206-208, 213. In view of these limitations, attention has turned to developing alternative staging methodologies through understanding differential gene expression in various stages of ovarian cancer and by obtaining various biomarkers to help better assess the progression of the disease. Vartiainen, J. *et al.*, *Int'l J. Cancer*, 95(5):313-16 (2001); Shridhar *et al. supra*; Baekelandt, M. *et al.*, *J. Clin. Oncol.* 18(22):3775-81.

The treatment of ovarian cancer typically involves a multiprong attack, with surgical intervention serving as the foundation of treatment. Dennis S. Chi & William J.

Hoskins, *Primary Surgical Management of Advanced Epithelial Ovarian Cancer*, in Ovarian Cancer 241 (Stephen C. Rubin & Gregory P. Sutton eds., 2d ed. 2001). For example, in the case of epithelial ovarian cancer, which accounts for ~90% of cases of ovarian cancer, treatment typically consists of: (1) cytoreductive surgery, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymphadenectomy, followed by (2) adjuvant chemotherapy with paclitaxel and either cisplatin or carboplatin. Eltabbakh, G.H. & Awtrey, C.S., *Expert Op. Pharmacother.* 2(10):109-24. Despite a clinical response rate of 80% to the adjuvant therapy, most patients experience tumor recurrence within three years of treatment. *Id.* Certain patients may undergo a second cytoreductive surgery and/or second-line chemotherapy. Memarzadeh & Berek, *supra*.

From the foregoing, it is clear that procedures used for detecting, diagnosing, monitoring, staging, prognosticating, and preventing the recurrence of ovarian cancer are of critical importance to the outcome of the patient. Moreover, current procedures, while helpful in each of these analyses, are limited by their specificity, sensitivity, invasiveness, and/or their cost. As such, highly specific and sensitive procedures that would operate by way of detecting novel markers in cells, tissues, or bodily fluids, with minimal invasiveness and at a reasonable cost, would be highly desirable.

As discussed above, each of the methods for diagnosing and staging ovarian, pancreatic or breast cancer is limited by the technology employed. Accordingly, there is need for sensitive molecular and cellular markers for the detection of ovarian, pancreatic or breast cancer. There is a need for molecular markers for the accurate staging, including clinical and pathological staging, of ovarian, pancreatic or breast cancers to optimize treatment methods. Finally, there is a need for sensitive molecular and cellular markers to monitor the progress of cancer treatments, including markers that can detect recurrence of ovarian, pancreatic or breast cancers following remission.

The present invention provides alternative methods of treating ovarian, pancreatic or breast cancer that overcome the limitations of conventional therapeutic methods as well as offer additional advantages that will be apparent from the detailed description below.

Growth and metastasis of solid tumors are also dependent on angiogenesis. Folkman, J., 1986, *Cancer Research*, 46, 467-473; Folkman, J., 1989, *Journal of the National Cancer Institute*, 82, 4-6. It has been shown, for example, that tumors which enlarge to greater than 2 mm must obtain their own blood supply and do so by inducing

the growth of new capillary blood vessels. Once these new blood vessels become embedded in the tumor, they provide a means for tumor cells to enter the circulation and metastasize to distant sites such as liver, lung or bone. Weidner, N., *et al.*, 1991, *The New England Journal of Medicine*, 324(1), 1-8.

5 Angiogenesis, defined as the growth or sprouting of new blood vessels from existing vessels, is a complex process that primarily occurs during embryonic development. The process is distinct from vasculogenesis, in that the new endothelial cells lining the vessel arise from proliferation of existing cells, rather than differentiating from stem cells. The process is invasive and dependent upon proteolysis of the extracellular
10 matrix (ECM), migration of new endothelial cells, and synthesis of new matrix components. Angiogenesis occurs during embryogenic development of the circulatory system; however, in adult humans, angiogenesis only occurs as a response to a pathological condition (except during the reproductive cycle in women).

Under normal physiological conditions in adults, angiogenesis takes place only in
15 very restricted situations such as hair growth and wounding healing. Auerbach, W. and Auerbach, R., 1994, *Pharmacol Ther.* 63(3):265-3 11; Ribatti et al., 1991, *Haematologica* 76(4):3 11-20; Risau, 1997, *Nature* 386(6626):67 1-4. Angiogenesis progresses by a stimulus which results in the formation of a migrating column of endothelial cells. Proteolytic activity is focused at the advancing tip of this "vascular sprout", which breaks
20 down the ECM sufficiently to permit the column of cells to infiltrate and migrate. Behind the advancing front, the endothelial cells differentiate and begin to adhere to each other, thus forming a new basement membrane. The cells then cease proliferation and finally define a lumen for the new arteriole or capillary.

Unregulated angiogenesis has gradually been recognized to be responsible for a
25 wide range of disorders, including, but not limited to, cancer, cardiovascular disease, rheumatoid arthritis, psoriasis and diabetic retinopathy. Folkman, 1995, *Nat Med* 1(1):27-31; Isner, 1999, *Circulation* 99(13): 1653-5; Koch, 1998, *Arthritis Rheum* 41(6):951-62; Walsh, 1999, *Rheumatology* (Oxford) 38(2):103-12; Ware and Simons, 1997, *Nat Med* 3(2): 158-64.

30 Of particular interest is the observation that angiogenesis is required by solid tumors for their growth and metastases. Folkman, 1986 *supra*; Folkman 1990, *J Natl Cancer Inst.*, 82(1) 4-6; Folkman, 1992, *Semin Cancer Biol* 3(2):65-71; Zetter, 1998, *Annu Rev Med* 49:407-24. A tumor usually begins as a single aberrant cell which can proliferate

only to a size of a few cubic millimeters due to the distance from available capillary beds, and it can stay 'dormant' without further growth and dissemination for a long period of time. Some tumor cells then switch to the angiogenic phenotype to activate endothelial cells, which proliferate and mature into new capillary blood vessels. These newly formed blood vessels not only allow for continued growth of the primary tumor, but also for the dissemination and recolonization of metastatic tumor cells. The precise mechanisms that control the angiogenic switch is not well understood, but it is believed that neovascularization of tumor mass results from the net balance of a multitude of angiogenesis stimulators and inhibitors Folkman, 1995, *supra*.

- 10 One of the most potent angiogenesis inhibitors is endostatin identified by O'Reilly and Folkman. O'Reilly et al., 1997, *Cell* 88(2):277-85; O'Reilly et al., 1994, *Cell* 79(2):3 15-28. Its discovery was based on the phenomenon that certain primary tumors can inhibit the growth of distant metastases. O'Reilly and Folkman hypothesized that a primary tumor initiates angiogenesis by generating angiogenic stimulators in excess of inhibitors.
- 15 However, angiogenic inhibitors, by virtue of their longer half life in the circulation, reach the site of a secondary tumor in excess of the stimulators. The net result is the growth of primary tumor and inhibition of secondary tumor. Endostatin is one of a growing list of such angiogenesis inhibitors produced by primary tumors. It is a proteolytic fragment of a larger protein: endostatin is a 20 kDa fragment of collagen XVIII (amino acid H1132-K1315 in murine collagen XVIII). Endostatin has been shown to specifically inhibit endothelial cell proliferation in vitro and block angiogenesis in vivo. More importantly, administration of endostatin to tumor-bearing mice leads to significant tumor regression, and no toxicity or drug resistance has been observed even after multiple treatment cycles. Boehm et al., 1997, *Nature* 390(6658):404-407. The fact that endostatin targets genetically stable endothelial cells and inhibits a variety of solid tumors makes it a very attractive candidate for anticancer therapy. Fidler and Ellis, 1994, *Cell* 79(2):185-8; Gastl et al., 1997, *Oncology* 54(3):177-84; Hinsbergh et al., 1999, *Ann Oncol* 10 Suppl 4:60-3. In addition, angiogenesis inhibitors have been shown to be more effective when combined with radiation and chemotherapeutic agents. Klement, 2000, *J. Clin Invest*, 105(8) R15-24. Browder, 2000, *Cancer Res*. 6-(7) 1878-86, Arap et al., 1998, *Science* 279(5349):377-80; Mauceri et al., 1998, *Nature* 394(6690):287-91.

SUMMARY OF THE INVENTION

The present invention solves many needs in the art by providing nucleic acid molecules, polypeptides and antibodies thereto, variants and derivatives of the nucleic acids and polypeptides, and agonists and antagonists thereto that may be used to identify, diagnose, monitor, stage, image and treat breast cancer and/or non-cancerous disease states in breast; identify and monitor breast tissue; and identify and design agonists and antagonists of polypeptides of the invention. The invention also provides gene therapy, methods for producing transgenic animals and cells, and methods for producing 10 engineered breast tissue for treatment and research.

One aspect of the present invention relates to nucleic acid molecules that are specific to breast cells, breast tissue and/or the breast organ. These breast specific nucleic acids (BSNAs) may be a naturally occurring cDNA, genomic DNA, RNA, or a fragment of one of these nucleic acids, or may be a non-naturally occurring nucleic acid molecule. 15 If the BSNA is genomic DNA, then the BSNA is a breast specific gene (BSG). If the BSNA is RNA, then it is a breast specific transcript encoded by a BSG. Due to alternative splicing and transcriptional modification one BSG may encode for multiple breast specific RNAs. In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that is specific to breast. More preferred is a nucleic acid molecule that encodes a polypeptide 20 comprising an amino acid sequence of SEQ ID NO: 73-179. In another preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1-72. For the BSNA sequences listed herein, DEX0451_001.nt.1 corresponds to SEQ ID NO: 1. For sequences with multiple splice variants, the parent sequence DEX0451_001.nt.1, will be followed by DEX0451_001.nt.2, etc. for each splice variant. 25 The sequences off the corresponding peptides are listed as DEX0451_001.aa.1, etc. For the mapping of all of the nucleotides and peptides, see the table in the Example 1 section below.

This aspect of the present invention also relates to nucleic acid molecules that selectively hybridize or exhibit substantial sequence similarity to nucleic acid molecules 30 encoding a breast Specific Protein (BSP), or that selectively hybridize or exhibit substantial sequence similarity to a BSNA. In one embodiment of the present invention the nucleic acid molecule comprises an allelic variant of a nucleic acid molecule encoding

a BSP, or an allelic variant of a BSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid sequence that encodes a BSP or a part of a nucleic acid sequence of a BSNA.

In addition, this aspect of the present invention relates to a nucleic acid molecule
5 further comprising one or more expression control sequences controlling the transcription
and/or translation of all or a part of a BSNA or the transcription and/or translation of a
nucleic acid molecule that encodes all or a fragment of a BSP.

Another aspect of the present invention relates to vectors and/or host cells
comprising a nucleic acid molecule of this invention. In a preferred embodiment, the
10 nucleic acid molecule of the vector and/or host cell encodes all or a fragment of a BSP. In
another preferred embodiment, the nucleic acid molecule of the vector and/or host cell
comprises all or a part of a BSNA. Vectors and host cells of the present invention are
useful in the recombinant production of polypeptides, particularly BSPs of the present
invention.

15 Another aspect of the present invention relates to polypeptides encoded by a
nucleic acid molecule of this invention. The polypeptide may comprise either a fragment
or a full-length protein. In a preferred embodiment, the polypeptide is a BSP. However,
this aspect of the present invention also relates to mutant proteins (muteins) of BSPs,
fusion proteins of which a portion is a BSP, and proteins and polypeptides encoded by
20 allelic variants of a BSNA as provided herein.

A further aspect of the present invention is a novel splice variant which encodes an
amino acid sequence that provides a novel region to be targeted for the generation of
reagents that can be used in the detection and/or treatment of cancer. The novel amino
acid sequence may lead to a unique protein structure, protein subcellular localization,
25 biochemical processing or function. This information can be used to directly or indirectly
facilitate the generation of additional or novel therapeutics or diagnostics. The nucleotide
sequence in this novel splice variant can be used as a nucleic acid probe for the diagnosis
and/or treatment of cancer.

Another aspect of the present invention relates to antibodies and other binders that
30 specifically bind to a polypeptide of the instant invention. Accordingly antibodies or
binders of the present invention specifically bind to BSPs, muteins, fusion proteins, and/or
homologous proteins or polypeptides encoded by allelic variants of a BSNA as provided
herein.

Another aspect of the present invention relates to agonists and antagonists of the nucleic acid molecules and polypeptides of this invention. The agonists and antagonists of the instant invention may be used to treat breast cancer and non-cancerous disease states in breast and to produce engineered breast tissue.

5 Another aspect of the present invention relates to methods for using the nucleic acid molecules to detect or amplify nucleic acid molecules that have similar or identical nucleic acid sequences compared to the nucleic acid molecules described herein. Such methods are useful in identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and/or non-cancerous disease states in breast. Such methods are also useful
10 10 in identifying and/or monitoring breast tissue. In addition, measurement of levels of one or more of the nucleic acid molecules of this invention may be useful as a diagnostic as part of a panel in combination with known other markers, particularly those described in the breast cancer background section above.

15 Another aspect of the present invention relates to use of the nucleic acid molecules of this invention in gene therapy, for producing transgenic animals and cells, and for producing engineered breast tissue for treatment and research.

20 Another aspect of the present invention relates to methods for detecting polypeptides of this invention, preferably using antibodies thereto. Such methods are useful to identify, diagnose, monitor, stage, image and treat breast cancer and/or non-cancerous disease states in breast. In addition, measurement of levels of one or more of the polypeptides of this invention may be useful to identify, diagnose, monitor, stage, and/or image breast cancer in combination with known other markers, particularly those described in the breast cancer background section above. The polypeptides of the present invention can also be used to identify and/or monitor breast tissue, and to produce
25 25 engineered breast tissue.

30 Yet another aspect of the present invention relates to a computer readable means of storing the nucleic acid and amino acid sequences of the invention. The records of the computer readable means can be accessed for reading and displaying of sequences for comparison, alignment and ordering of the sequences of the invention to other sequences. In addition, the computer records regarding the nucleic acid and/or amino acid sequences and/or measurements of their levels may be used alone or in combination with other markers to diagnose breast related diseases.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Techniques

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. *See, e.g.*, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press (1989) and Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 3d ed., Cold Spring Harbor Press (2001); Ausubel *et al.*, Current Protocols in Molecular Biology, Greene Publishing Associates (1992, and Supplements to 2000); Ausubel *et al.*, Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology – 4th Ed., Wiley & Sons (1999); Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1990); and Harlow and Lane, Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1999).

Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

The following terms, unless otherwise indicated, shall be understood to have the following meanings:

A "nucleic acid molecule" of this invention refers to a polymeric form of nucleotides and includes both sense and antisense strands of RNA, cDNA, genomic DNA,

and synthetic forms and mixed polymers of the above. A nucleotide refers to a ribonucleotide, deoxynucleotide or a modified form of either type of nucleotide. A "nucleic acid molecule" as used herein is synonymous with "nucleic acid" and "polynucleotide." The term "nucleic acid molecule" usually refers to a molecule of at least 10 bases in length, unless otherwise specified. The term includes single- and double-stranded forms of DNA. In addition, a polynucleotide may include either or both naturally occurring and modified nucleotides linked together by naturally occurring and/or non-naturally occurring nucleotide linkages.

Nucleotides are represented by single letter symbols in nucleic acid molecule sequences. The following table lists symbols identifying nucleotides or groups of nucleotides which may occupy the symbol position on a nucleic acid molecule. See Nomenclature Committee of the International Union of Biochemistry (NC-IUB), Nomenclature for incompletely specified bases in nucleic acid sequences, Recommendations 1984., *Eur J Biochem.* 150(1):1-5 (1985).

Symbol	Meaning	Group/Origin of Designation	Complementary Symbol
a	a	Adenine	t/u
g	g	Guanine	c
c	c	Cytosine	g
t	t	Thymine	a
u	u	Uracil	a
r	g or a	puRine	y
y	t/u or c	pYrimidine	r
m	a or c	aMino	k
k	g or t/u	Keto	m
s	g or c	Strong interactions 3H-bonds	w
w	a or t/u	Weak interactions 2H-bonds	s
b	g or c or t/u	not a	v
d	a or g or t/u	not c	h
h	a or c or t/u	not g	d
v	a or g or c	not t, not u	b
n	a or g or c or t/u, unknown, or other	aNy	n

15

The nucleic acid molecules may be modified chemically or biochemically or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those of skill in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoramidates, carbamates, etc.), charged linkages (e.g.,

- phosphorothioates, phosphorodithioates, etc.), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen, etc.), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids, etc.) The term “nucleic acid molecule” also includes any topological conformation, including single-stranded, double-stranded, partially duplexed, triplexed, hairpinned, circular and padlocked conformations. Also included are synthetic molecules that mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.
- 10 A “gene” is defined as a nucleic acid molecule that comprises a nucleic acid sequence that encodes a polypeptide and the expression control sequences that surround the nucleic acid sequence that encodes the polypeptide. For instance, a gene may comprise a promoter, one or more enhancers, a nucleic acid sequence that encodes a polypeptide, downstream regulatory sequences and, possibly, other nucleic acid sequences involved in regulation of the expression of an RNA. As is well known in the art, eukaryotic genes usually contain both exons and introns. The term “exon” refers to a nucleic acid sequence found in genomic DNA that is bioinformatically predicted and/or experimentally confirmed to contribute contiguous sequence to a mature mRNA transcript. The term “intron” refers to a nucleic acid sequence found in genomic DNA that is predicted and/or confirmed to not contribute to a mature mRNA transcript, but rather to be “spliced out” during processing of the transcript.
- 15 A nucleic acid molecule or polypeptide is “derived” from a particular species if the nucleic acid molecule or polypeptide has been isolated from the particular species, or if the nucleic acid molecule or polypeptide is homologous to a nucleic acid molecule or polypeptide isolated from a particular species.
- 20 An “isolated” or “substantially pure” nucleic acid or polynucleotide (*e.g.*, an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components that naturally accompany the native polynucleotide in its natural host cell, *e.g.*, ribosomes, polymerases, or genomic sequences with which it is naturally associated.
- 25 The term embraces a nucleic acid or polynucleotide that (1) has been removed from its naturally occurring environment, (2) is not associated with all or a portion of a polynucleotide in which the “isolated polynucleotide” is found in nature, (3) is operatively linked to a polynucleotide which it is not linked to in nature, (4) does not occur in nature

as part of a larger sequence or (5) includes nucleotides or internucleoside bonds that are not found in nature. The term “isolated” or “substantially pure” also can be used in reference to recombinant or cloned DNA isolates, chemically synthesized polynucleotide analogs, or polynucleotide analogs that are biologically synthesized by heterologous systems. The term “isolated nucleic acid molecule” includes nucleic acid molecules that are integrated into a host cell chromosome at a heterologous site, recombinant fusions of a native fragment to a heterologous sequence, recombinant vectors present as episomes or as integrated into a host cell chromosome.

A “part” of a nucleic acid molecule refers to a nucleic acid molecule that comprises a partial contiguous sequence of at least 10 bases of the reference nucleic acid molecule. Preferably, a part comprises at least 15 to 20 bases of a reference nucleic acid molecule. In theory, a nucleic acid sequence of 17 nucleotides is of sufficient length to occur at random less frequently than once in the three gigabase human genome, and thus provides a nucleic acid probe that can uniquely identify the reference sequence in a nucleic acid mixture of genomic complexity. A preferred part is one that comprises a nucleic acid sequence that can encode at least 6 contiguous amino acid sequences (fragments of at least 18 nucleotides) because they are useful in directing the expression or synthesis of peptides that are useful in mapping the epitopes of the polypeptide encoded by the reference nucleic acid. *See, e.g., Geysen et al., Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1984); and U.S. Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. A part may also comprise at least 25, 30, 35 or 40 nucleotides of a reference nucleic acid molecule, or at least 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides of a reference nucleic acid molecule. A part of a nucleic acid molecule may comprise no other nucleic acid sequences. Alternatively, a part of a nucleic acid may comprise other nucleic acid sequences from other nucleic acid molecules.

The term “oligonucleotide” refers to a nucleic acid molecule generally comprising a length of 200 bases or fewer. The term often refers to single-stranded deoxyribonucleotides, but it can refer as well to single-or double-stranded ribonucleotides, RNA:DNA hybrids and double-stranded DNAs, among others. Preferably, oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19 or 20 bases in length. Other preferred oligonucleotides are 25, 30, 35, 40, 45, 50, 55 or 60 bases in length. Oligonucleotides may be single-stranded, *e.g.* for use as probes

or primers, or may be double-stranded, *e.g.* for use in the construction of a mutant gene. Oligonucleotides of the invention can be either sense or antisense oligonucleotides. An oligonucleotide can be derivatized or modified as discussed above for nucleic acid molecules.

- 5 Oligonucleotides, such as single-stranded DNA probe oligonucleotides, often are synthesized by chemical methods, such as those implemented on automated oligonucleotide synthesizers. However, oligonucleotides can be made by a variety of other methods, including *in vitro* recombinant DNA-mediated techniques and by expression of DNAs in cells and organisms. Initially, chemically synthesized DNAs
- 10 typically are obtained without a 5' phosphate. The 5' ends of such oligonucleotides are not substrates for phosphodiester bond formation by ligation reactions that employ DNA ligases typically used to form recombinant DNA molecules. Where ligation of such oligonucleotides is desired, a phosphate can be added by standard techniques, such as those that employ a kinase and ATP. The 3' end of a chemically synthesized
- 15 oligonucleotide generally has a free hydroxyl group and, in the presence of a ligase, such as T4 DNA ligase, readily will form a phosphodiester bond with a 5' phosphate of another polynucleotide, such as another oligonucleotide. As is well known, this reaction can be prevented selectively, where desired, by removing the 5' phosphates of the other polynucleotide(s) prior to ligation.
- 20 The term "naturally occurring nucleotide" referred to herein includes naturally occurring deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "nucleotide linkages" referred to herein includes nucleotide linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate,
- 25 phosphoroanilothioate, phosphoranilate, phosphoroamidate, and the like. *See e.g.*, LaPlanche *et al.* *Nucl. Acids Res.* 14:9081-9093 (1986); Stein *et al.* *Nucl. Acids Res.* 16:3209-3221 (1988); Zon *et al.* *Anti-Cancer Drug Design* 6:539-568 (1991); Zon *et al.*, in Eckstein (ed.) Oligonucleotides and Analogues: A Practical Approach, pp. 87-108, Oxford University Press (1991); Uhlmann and Peyman *Chemical Reviews* 90:543 (1990),
- 30 and U.S. Patent No. 5,151,510, the disclosure of which is hereby incorporated by reference in its entirety.

Unless specified otherwise, the left hand end of a polynucleotide sequence in sense orientation is the 5' end and the right hand end of the sequence is the 3' end. In addition,

the left hand direction of a polynucleotide sequence in sense orientation is referred to as the 5' direction, while the right hand direction of the polynucleotide sequence is referred to as the 3' direction. Further, unless otherwise indicated, each nucleotide sequence is set forth herein as a sequence of deoxyribonucleotides. It is intended, however, that the given sequence be interpreted as would be appropriate to the polynucleotide composition: for example, if the isolated nucleic acid is composed of RNA, the given sequence intends ribonucleotides, with uridine substituted for thymidine.

The term "allelic variant" refers to one of two or more alternative naturally occurring forms of a gene, wherein each gene possesses a unique nucleotide sequence. In a preferred embodiment, different alleles of a given gene have similar or identical biological properties.

The term "percent sequence identity" in the context of nucleic acid sequences refers to the residues in two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over a stretch of at least about nine nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number of different algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using FASTA, Gap or Bestfit, which are programs in Wisconsin Package Version 10.0, Genetics Computer Group (GCG), Madison, Wisconsin. FASTA, which includes, e.g., the programs FASTA2 and FASTA3, provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.* 183: 63-98 (1990); Pearson, *Methods Mol. Biol.* 132: 185-219 (2000); Pearson, *Methods Enzymol.* 266: 227-258 (1996); Pearson, *J. Mol. Biol.* 276: 71-84 (1998)). Unless otherwise specified, default parameters for a particular program or algorithm are used. For instance, percent sequence identity between nucleic acid sequences can be determined using FASTA with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) or using Gap with its default parameters as provided in GCG Version 6.1.

A reference to a nucleic acid sequence encompasses its complement unless otherwise specified. Thus, a reference to a nucleic acid molecule having a particular sequence should be understood to encompass its complementary strand, with its complementary sequence. The complementary strand is also useful, e.g., for antisense

therapy, double-stranded RNA (dsRNA) inhibition (RNAi), combination of triplex and antisense, hybridization probes and PCR primers.

In the molecular biology art, researchers use the terms "percent sequence identity", "percent sequence similarity" and "percent sequence homology" interchangeably. In this application, these terms shall have the same meaning with respect to nucleic acid sequences only.

The term "substantial similarity" or "substantial sequence similarity," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 50%, more preferably 60% of the nucleotide bases, usually at least about 70%, more usually at least about 80%, preferably at least about 90%, and more preferably at least about 95-98% of the nucleotide bases, as measured by any well known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed above.

Alternatively, substantial similarity exists between a first and second nucleic acid sequence when the first nucleic acid sequence or fragment thereof hybridizes to an antisense strand of the second nucleic acid, under selective hybridization conditions. Typically, selective hybridization will occur between the first nucleic acid sequence and an antisense strand of the second nucleic acid sequence when there is at least about 55% sequence identity between the first and second nucleic acid sequences—preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%—over a stretch of at least about 14 nucleotides, more preferably at least 17 nucleotides, even more preferably at least 20, 25, 30, 35, 40, 50, 60, 70, 80, 90 or 100 nucleotides.

Nucleic acid hybridization will be affected by such conditions as salt concentration, temperature, solvents, the base composition of the hybridizing species, length of the complementary regions, and the number of nucleotide base mismatches between the hybridizing nucleic acids, as will be readily appreciated by those skilled in the art. "Stringent hybridization conditions" and "stringent wash conditions" in the context of nucleic acid hybridization experiments depend upon a number of different physical parameters. The most important parameters include temperature of hybridization, base composition of the nucleic acids, salt concentration and length of the nucleic acid. One having ordinary skill in the art knows how to vary these parameters to achieve a particular stringency of hybridization. In general, "stringent hybridization" is performed at about

25°C below the thermal melting point (T_m) for the specific DNA hybrid under a particular set of conditions. "Stringent washing" is performed at temperatures about 5°C lower than the T_m for the specific DNA hybrid under a particular set of conditions. The T_m is the temperature at which 50% of the target sequence hybridizes to a perfectly matched probe.

5 See Sambrook (1989), *supra*, p. 9.51.

The T_m for a particular DNA-DNA hybrid can be estimated by the formula:

$$T_m = 81.5^{\circ}\text{C} + 16.6 (\log_{10}[\text{Na}^+]) + 0.41 (\text{fraction G} + \text{C}) - 0.63 (\%) \text{ formamide} - (600/l) \text{ where } l \text{ is the length of the hybrid in base pairs.}$$

The T_m for a particular RNA-RNA hybrid can be estimated by the formula:

10 $T_m = 79.8^{\circ}\text{C} + 18.5 (\log_{10}[\text{Na}^+]) + 0.58 (\text{fraction G} + \text{C}) + 11.8 (\text{fraction G} + \text{C})^2 - 0.35 (\%) \text{ formamide} - (820/l).$

The T_m for a particular RNA-DNA hybrid can be estimated by the formula:

$$T_m = 79.8^{\circ}\text{C} + 18.5(\log_{10}[\text{Na}^+]) + 0.58 (\text{fraction G} + \text{C}) + 11.8 (\text{fraction G} + \text{C})^2 - 0.50 (\%) \text{ formamide} - (820/l).$$

15 In general, the T_m decreases by 1-1.5°C for each 1% of mismatch between two nucleic acid sequences. Thus, one having ordinary skill in the art can alter hybridization and/or washing conditions to obtain sequences that have higher or lower degrees of sequence identity to the target nucleic acid. For instance, to obtain hybridizing nucleic acids that contain up to 10% mismatch from the target nucleic acid sequence, 10-15°C would be subtracted from the calculated T_m of a perfectly matched hybrid, and then the hybridization and washing temperatures adjusted accordingly. Probe sequences may also hybridize specifically to duplex DNA under certain conditions to form triplex or other higher order DNA complexes. The preparation of such probes and suitable hybridization conditions are well known in the art.

20

25 An example of stringent hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100 complementary residues on a filter in a Southern or Northern blot or for screening a library is 50% formamide/6X SSC at 42°C for at least ten hours and preferably overnight (approximately 16 hours). Another example of stringent hybridization conditions is 6X SSC at 68°C without formamide for at least ten hours and preferably overnight. An example of moderate stringency hybridization conditions is 6X SSC at 55°C without formamide for at least ten hours and preferably overnight. An example of low stringency hybridization conditions for hybridization of complementary nucleic acid sequences having more than 100

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complementary residues on a filter in a Southern or northern blot or for screening a library is 6X SSC at 42°C for at least ten hours. Hybridization conditions to identify nucleic acid sequences that are similar but not identical can be identified by experimentally changing the hybridization temperature from 68°C to 42°C while keeping the salt concentration 5 constant (6X SSC), or keeping the hybridization temperature and salt concentration constant (e.g. 42°C and 6X SSC) and varying the formamide concentration from 50% to 0%. Hybridization buffers may also include blocking agents to lower background. These agents are well known in the art. See Sambrook *et al.* (1989), *supra*, pages 8.46 and 9.46-9.58. See also Ausubel (1992), *supra*, Ausubel (1999), *supra*, and Sambrook (2001), 10 *supra*.

Wash conditions also can be altered to change stringency conditions. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (see Sambrook (1989), *supra*, for SSC buffer). Often the high stringency wash is preceded by a low stringency wash to remove excess probe. An exemplary medium stringency wash for 15 duplex DNA of more than 100 base pairs is 1x SSC at 45°C for 15 minutes. An exemplary low stringency wash for such a duplex is 4x SSC at 40°C for 15 minutes. In general, signal-to-noise ratio of 2x or higher than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization.

As defined herein, nucleic acids that do not hybridize to each other under stringent 20 conditions are still substantially similar to one another if they encode polypeptides that are substantially identical to each other. This occurs, for example, when a nucleic acid is created synthetically or recombinantly using a high codon degeneracy as permitted by the redundancy of the genetic code.

Hybridization conditions for nucleic acid molecules that are shorter than 100 25 nucleotides in length (e.g., for oligonucleotide probes) may be calculated by the formula: $T_m = 81.5^{\circ}\text{C} + 16.6(\log_{10}[\text{Na}^+]) + 0.41(\text{fraction G+C}) - (600/N)$, wherein N is change length and the $[\text{Na}^+]$ is 1 M or less. See Sambrook (1989), *supra*, p. 11.46. For hybridization of probes shorter than 100 nucleotides, hybridization is usually performed under stringent conditions (5-10°C below the T_m) using high concentrations (0.1-1.0 30 pmol/ml) of probe. *Id.* at p. 11.45. Determination of hybridization using mismatched probes, pools of degenerate probes or "guessmers," as well as hybridization solutions and methods for empirically determining hybridization conditions are well known in the art. See, e.g., Ausubel (1999), *supra*; Sambrook (1989), *supra*, pp. 11.45-11.57.

The term "digestion" or "digestion of DNA" refers to catalytic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The various restriction enzymes referred to herein are commercially available and their reaction conditions, cofactors and other requirements for use are known and routine to the skilled artisan. For analytical purposes, typically, 1 µg of plasmid or DNA fragment is digested with about 2 units of enzyme in about 20 µl of reaction buffer. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 µg of DNA are digested with 20 to 250 units of enzyme in proportionately larger volumes. Appropriate buffers and substrate amounts for particular restriction enzymes are described in standard laboratory manuals, such as those referenced below, and are specified by commercial suppliers. Incubation times of about 1 hour at 37°C are ordinarily used, but conditions may vary in accordance with standard procedures, the supplier's instructions and the particulars of the reaction. After digestion, reactions may be analyzed, and fragments may be purified by electrophoresis through an agarose or polyacrylamide gel, using well known methods that are routine for those skilled in the art.

The term "ligation" refers to the process of forming phosphodiester bonds between two or more polynucleotides, which most often are double-stranded DNAs. Techniques for ligation are well known to the art and protocols for ligation are described in standard laboratory manuals and references, such as, *e.g.*, Sambrook (1989), *supra*.

Genome-derived "single exon probes," are probes that comprise at least part of an exon ("reference exon") and can hybridize detectably under high stringency conditions to transcript-derived nucleic acids that include the reference exon but do not hybridize detectably under high stringency conditions to nucleic acids that lack the reference exon. Single exon probes typically further comprise, contiguous to a first end of the exon portion, a first intronic and/or intergenic sequence that is identically contiguous to the exon in the genome, and may contain a second intronic and/or intergenic sequence that is identically contiguous to the exon in the genome. The minimum length of genome-derived single exon probes is defined by the requirement that the exonic portion be of sufficient length to hybridize under high stringency conditions to transcript-derived nucleic acids, as discussed above. The maximum length of genome-derived single exon probes is defined by the requirement that the probes contain portions of no more than one exon. The single exon probes may contain priming sequences not found in contiguity with the rest of the probe sequence in the genome, which priming sequences are useful for PCR

and other amplification-based technologies. In another aspect, the invention is directed to single exon probes based on the BSNAs disclosed herein.

- In one embodiment, the term “microarray” refers to a “nucleic acid microarray” having a substrate-bound plurality of nucleic acids, hybridization to each of the plurality of bound nucleic acids being separately detectable. The substrate can be solid or porous, planar or non-planar, unitary or distributed. Nucleic acid microarrays include all the devices so called in Schena (ed.), DNA Microarrays: A Practical Approach (Practical Approach Series), Oxford University Press (1999); *Nature Genet.* 21(1)(suppl.):1 - 60 (1999); Schena (ed.), Microarray Biochip: Tools and Technology, Eaton Publishing Company/BioTechniques Books Division (2000). Additionally, these nucleic acid microarrays include a substrate-bound plurality of nucleic acids in which the plurality of nucleic acids are disposed on a plurality of beads, rather than on a unitary planar substrate, as is described, *inter alia*, in Brenner *et al.*, *Proc. Natl. Acad. Sci. USA* 97(4):1665-1670 (2000). Examples of nucleic acid microarrays may be found in U.S. Patent Nos. 6,391,623, 6,383,754, 6,383,749, 6,380,377, 6,379,897, 6,376,191, 6,372,431, 6,351,712, 6,344,316, 6,316,193, 6,312,906, 6,309,828, 6,309,824, 6,306,643, 6,300,063, 6,287,850, 6,284,497, 6,284,465, 6,280,954, 6,262,216, 6,251,601, 6,245,518, 6,263,287, 6,251,601, 6,238,866, 6,228,575, 6,214,587, 6,203,989, 6,171,797, 6,103,474, 6,083,726, 6,054,274, 6,040,138, 6,083,726, 6,004,755, 6,001,309, 5,958,342, 5,952,180, 5,936,731, 5,843,655, 5,814,454, 5,837,196, 5,436,327, 5,412,087, and 5,405,783, the disclosures of which are incorporated herein by reference in their entireties.
- In an alternative embodiment, a “microarray” may also refer to a “peptide microarray” or “protein microarray” having a substrate-bound collection or plurality of polypeptides, the binding to each of the plurality of bound polypeptides being separately detectable. Alternatively, the peptide microarray may have a plurality of binders, including but not limited to monoclonal antibodies, polyclonal antibodies, phage display binders, yeast 2 hybrid binders, and aptamers, which can specifically detect the binding of the polypeptides of this invention. The array may be based on autoantibody detection to the polypeptides of this invention, see Robinson *et al.*, *Nature Medicine* 8(3):295-301 (2002). Examples of peptide arrays may be found in WO 02/31463, WO 02/25288, WO 01/94946, WO 01/88162, WO 01/68671, WO 01/57259, WO 00/61806, WO 00/54046, WO 00/47774, WO 99/40434, WO 99/39210, and WO 97/42507 and U.S. Patent Nos.

6,268,210, 5,766,960, and 5,143,854, the disclosures of which are incorporated herein by reference in their entireties.

In addition, determination of the levels of the BSNA or BSP may be made in a multiplex manner using techniques described in WO 02/29109, WO 02/24959, WO 5 01/83502, WO01/73113, WO 01/59432, WO 01/57269, and WO 99/67641, the disclosures of which are incorporated herein by reference in their entireties.

The term "mutant", "mutated", or "mutation" when applied to nucleic acid sequences means that nucleotides in a nucleic acid sequence may be inserted, deleted or changed compared to a reference nucleic acid sequence. A single alteration may be made 10 at a locus (a point mutation) or multiple nucleotides may be inserted, deleted or changed at a single locus. In addition, one or more alterations may be made at any number of loci within a nucleic acid sequence. In a preferred embodiment of the present invention, the nucleic acid sequence is the wild type nucleic acid sequence encoding a BSP or is a BSNA. The nucleic acid sequence may be mutated by any method known in the art 15 including those mutagenesis techniques described *infra*.

The term "error-prone PCR" refers to a process for performing PCR under conditions where the copying fidelity of the DNA polymerase is low, such that a high rate of point mutations is obtained along the entire length of the PCR product. *See, e.g., Leung et al., Technique 1: 11-15 (1989)* and *Caldwell et al., PCR Methods Applic. 2: 28-33 (1992)*.

The term "oligonucleotide-directed mutagenesis" refers to a process which enables the generation of site-specific mutations in any cloned DNA segment of interest. *See, e.g., Reidhaar-Olson et al., Science 241: 53-57 (1988)*.

The term "assembly PCR" refers to a process which involves the assembly of a 25 PCR product from a mixture of small DNA fragments. A large number of different PCR reactions occur in parallel in the same vial, with the products of one reaction priming the products of another reaction.

The term "sexual PCR mutagenesis" or "DNA shuffling" refers to a method of error-prone PCR coupled with forced homologous recombination between DNA 30 molecules of different but highly related DNA sequence *in vitro*, caused by random fragmentation of the DNA molecule based on sequence similarity, followed by fixation of the crossover by primer extension in an error-prone PCR reaction. *See, e.g., Stemmer,*

Proc. Natl. Acad. Sci. U.S.A. 91: 10747-10751 (1994). DNA shuffling can be carried out between several related genes (“Family shuffling”).

The term “*in vivo* mutagenesis” refers to a process of generating random mutations in any cloned DNA of interest which involves the propagation of the DNA in a strain of bacteria such as *E. coli* that carries mutations in one or more of the DNA repair pathways. These “mutator” strains have a higher random mutation rate than that of a wild-type parent. Propagating the DNA in a mutator strain will eventually generate random mutations within the DNA.

The term “cassette mutagenesis” refers to any process for replacing a small region of a double-stranded DNA molecule with a synthetic oligonucleotide “cassette” that differs from the native sequence. The oligonucleotide often contains completely and/or partially randomized native sequence.

The term “recursive ensemble mutagenesis” refers to an algorithm for protein engineering (protein mutagenesis) developed to produce diverse populations of phenotypically related mutants whose members differ in amino acid sequence. This method uses a feedback mechanism to control successive rounds of combinatorial cassette mutagenesis. *See, e.g., Arkin et al., Proc. Natl. Acad. Sci. U.S.A.* 89: 7811-7815 (1992).

The term “exponential ensemble mutagenesis” refers to a process for generating combinatorial libraries with a high percentage of unique and functional mutants, wherein small groups of residues are randomized in parallel to identify, at each altered position, amino acids which lead to functional proteins. *See, e.g., Delegrave et al., Biotechnology Research* 11: 1548-1552 (1993); Arnold, *Current Opinion in Biotechnology* 4: 450-455 (1993).

“Operatively linked” expression control sequences refers to a linkage in which the expression control sequence is either contiguous with the gene of interest to control the gene of interest, or acts in *trans* or at a distance to control the gene of interest.

The term “expression control sequence” as used herein refers to polynucleotide sequences which are necessary to affect the expression of coding sequences to which they are operatively linked. Expression control sequences are sequences which control the transcription, post-transcriptional events and translation of nucleic acid sequences. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that

enhance translation efficiency (*e.g.*, ribosome binding sites); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription 5 termination sequence. The term “control sequences” is intended to include, at a minimum, all components whose presence is essential for expression, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences.

The term “vector,” as used herein, is intended to refer to a nucleic acid molecule 10 capable of transporting another nucleic acid to which it has been linked. One type of vector is a “plasmid”, which refers to a circular double-stranded DNA loop into which additional DNA segments may be ligated. Other vectors include cosmids, bacterial artificial chromosomes (BAC) and yeast artificial chromosomes (YAC). Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral 15 genome. Viral vectors that infect bacterial cells are referred to as bacteriophages. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication). Other vectors can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of 20 directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors” (or simply, “expression vectors”). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, “plasmid” and “vector” may be used interchangeably as the plasmid is the most commonly used form of vector. However, the 25 invention is intended to include other forms of expression vectors that serve equivalent functions.

The term “recombinant host cell” (or simply “host cell”), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular 30 subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term “host cell” as used herein.

As used herein, the phrase “open reading frame” and the equivalent acronym “ORF” refers to that portion of a transcript-derived nucleic acid that can be translated in its entirety into a sequence of contiguous amino acids. As so defined, an ORF has length, measured in nucleotides, exactly divisible by 3. As so defined, an ORF need not encode 5 the entirety of a natural protein.

As used herein, the phrase “ORF-encoded peptide” refers to the predicted or actual translation of an ORF.

As used herein, the phrase “degenerate variant” of a reference nucleic acid sequence is meant to be inclusive of all nucleic acid sequences that can be directly 10 translated, using the standard genetic code, to provide an amino acid sequence identical to that translated from the reference nucleic acid sequence.

The term “polypeptide” encompasses both naturally occurring and non-naturally occurring proteins and polypeptides, as well as polypeptide fragments and polypeptide mutants, derivatives and analogs thereof. A polypeptide may be monomeric or polymeric. 15 Further, a polypeptide may comprise a number of different modules within a single polypeptide each of which has one or more distinct activities. A preferred polypeptide in accordance with the invention comprises a BSP encoded by a nucleic acid molecule of the instant invention, or a fragment, mutant, analog or derivative thereof.

The term “isolated protein” or “isolated polypeptide” is a protein or polypeptide 20 that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is free of other proteins from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be “isolated” 25 from its naturally associated components. A polypeptide or protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

A protein or polypeptide is “substantially pure,” “substantially homogeneous” or “substantially purified” when at least about 60% to 75% of a sample exhibits a single 30 species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A substantially pure polypeptide or protein will typically comprise about 50%, 60%, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be determined by a number of means

well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel with a stain well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

5 The term "fragment" when used herein with respect to polypeptides of the present invention refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion compared to a full-length BSP. In a preferred embodiment, the fragment is a contiguous sequence in which the amino acid sequence of the fragment is identical to the corresponding positions in the naturally occurring polypeptide. Fragments typically are at
10 least 5, 6, 7, 8, 9 or 10 amino acids long, preferably at least 12, 14, 16 or 18 amino acids long, more preferably at least 20 amino acids long, more preferably at least 25, 30, 35, 40 or 45, amino acids, even more preferably at least 50 or 60 amino acids long, and even more preferably at least 70 amino acids long.

A "derivative" when used herein with respect to polypeptides of the present
15 invention refers to a polypeptide which is substantially similar in primary structural sequence to a BSP but which includes, *e.g.*, *in vivo* or *in vitro* chemical and biochemical modifications that are not found in the BSP. Such modifications include, for example, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide
20 derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing,
25 phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. Other modifications include, *e.g.*, labeling with radionuclides, and various enzymatic modifications, as will be readily appreciated by those skilled in the art. A variety of methods for labeling polypeptides and of substituents or labels useful for such purposes
30 are well known in the art, and include radioactive isotopes such as ^{125}I , ^{32}P , ^{35}S , ^{14}C and ^3H , ligands which bind to labeled antiligands (*e.g.*, antibodies), fluorophores, chemiluminescent agents, enzymes, and antiligands which can serve as specific binding pair members for a labeled ligand. The choice of label depends on the sensitivity required,

ease of conjugation with the primer, stability requirements, and available instrumentation. Methods for labeling polypeptides are well known in the art. See Ausubel (1992), *supra*; Ausubel (1999), *supra*.

The term "fusion protein" refers to polypeptides of the present invention coupled 5 to a heterologous amino acid sequence. Fusion proteins are useful because they can be constructed to contain two or more desired functional elements from two or more different proteins. A fusion protein comprises at least 10 contiguous amino acids from a polypeptide of interest, more preferably at least 20 or 30 amino acids, even more preferably at least 40, 50 or 60 amino acids, yet more preferably at least 75, 100 or 125 10 amino acids. Fusion proteins can be produced recombinantly by constructing a nucleic acid sequence that encodes the polypeptide or a fragment thereof in frame with a nucleic acid sequence encoding a different protein or peptide and then expressing the fusion protein. Alternatively, a fusion protein can be produced chemically by crosslinking the polypeptide or a fragment thereof to another protein.

15 The term "analog" refers to both polypeptide analogs and non-peptide analogs. The term "polypeptide analog" as used herein refers to a polypeptide that is comprised of a segment of at least 25 amino acids that has substantial identity to a portion of an amino acid sequence but which contains non-natural amino acids or non-natural inter-residue bonds. In a preferred embodiment, the analog has the same or similar biological activity 20 as the native polypeptide. Typically, polypeptide analogs comprise a conservative amino acid substitution (or insertion or deletion) with respect to the naturally occurring sequence. Analogs typically are at least 20 amino acids long, preferably at least 50 amino acids long or longer, and can often be as long as a full-length naturally occurring polypeptide.

The term "non-peptide analog" refers to a compound with properties that are 25 analogous to those of a reference polypeptide. A non-peptide compound may also be termed a "peptide mimetic" or a "peptidomimetic." Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to useful peptides may be used to produce an equivalent effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that 30 has a desired biochemical property or pharmacological activity), but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of:
--CH₂NH--, --CH₂S--, --CH₂-CH₂--, --CH=CH--(cis and trans), --COCH₂--,
--CH(OH)CH₂--, and --CH₂SO--, by methods well known in the art. Systematic

substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known 5 in the art (Rizo *et al.*, *Ann. Rev. Biochem.* 61:387-418 (1992)). For example, one may add internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

The term "mutant" or "mutein" when referring to a polypeptide of the present invention relates to an amino acid sequence containing substitutions, insertions or 10 deletions of one or more amino acids compared to the amino acid sequence of a BSP. A mutein may have one or more amino acid point substitutions, in which a single amino acid at a position has been changed to another amino acid, one or more insertions and/or deletions, in which one or more amino acids are inserted or deleted, respectively, in the sequence of the naturally occurring protein, and/or truncations of the amino acid sequence 15 at either or both the amino or carboxy termini. Further, a mutein may have the same or different biological activity as the naturally occurring protein. For instance, a mutein may have an increased or decreased biological activity. A mutein has at least 50% sequence similarity to the wild type protein, preferred is 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are muteins having 80%, 85% or 90% 20 sequence similarity to a BSP. In an even more preferred embodiment, a mutein exhibits 95% sequence identity, even more preferably 97%, even more preferably 98% and even more preferably 99%. Sequence similarity may be measured by any common sequence analysis algorithm, such as GAP or BESTFIT or other variation Smith-Waterman alignment. *See*, T. F. Smith and M. S. Waterman, *J. Mol. Biol.* 147:195-197 (1981) and 25 W.R. Pearson, *Genomics* 11:635-650 (1991).

Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinity or enzymatic activity, and (5) confer or modify other physicochemical or functional properties of such analogs. For example, 30 single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. In a preferred embodiment, the amino acid substitutions are moderately conservative substitutions or

conservative substitutions. In a more preferred embodiment, the amino acid substitutions are conservative substitutions. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (*e.g.*, a replacement amino acid should not tend to disrupt a helix that occurs in the parent 5 sequence, or disrupt other types of secondary structure that characterize the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in Creighton (ed.), *Proteins, Structures and Molecular Principles*, W. H. Freeman and Company (1984); Branden *et al.* (ed.), *Introduction to Protein Structure*, Garland Publishing (1991); Thornton *et al.*, *Nature* 354:105-106 (1991).

10 As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. *See* Golub *et al.* (eds.), *Immunology - A Synthesis* 2nd Ed., Sinauer Associates (1991). Stereoisomers (*e.g.*, D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α -, α -disubstituted amino acids, N-alkyl amino acids, and other unconventional amino acids may also be suitable components for polypeptides 15 of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, s-N-methylarginine, and other similar amino acids and imino acids (*e.g.*, 4-hydroxyproline). In the polypeptide notation used herein, the lefthand direction is the 20 amino terminal direction and the right hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

By "homology" or "homologous" when referring to a polypeptide of the present invention it is meant polypeptides from different organisms with a similar sequence to the encoded amino acid sequence of a BSP and a similar biological activity or function. 25 Although two polypeptides are said to be "homologous," this does not imply that there is necessarily an evolutionary relationship between the polypeptides. Instead, the term "homologous" is defined to mean that the two polypeptides have similar amino acid sequences and similar biological activities or functions. In a preferred embodiment, a homologous polypeptide is one that exhibits 50% sequence similarity to BSP, preferred is 30 60% sequence similarity, more preferred is 70% sequence similarity. Even more preferred are homologous polypeptides that exhibit 80%, 85% or 90% sequence similarity to a BSP. In yet a more preferred embodiment, a homologous polypeptide exhibits 95%, 97%, 98% or 99% sequence similarity.

When “sequence similarity” is used in reference to polypeptides, it is recognized that residue positions that are not identical often differ by conservative amino acid substitutions. In a preferred embodiment, a polypeptide that has “sequence similarity” comprises conservative or moderately conservative amino acid substitutions. A 5 “conservative amino acid substitution” is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative 10 substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, e.g., Pearson, *Methods Mol. Biol.* 24: 307-31 (1994).

For instance, the following six groups each contain amino acids that are 15 conservative substitutions for one another:

- 1) Serine (S), Threonine (T);
- 2) Aspartic Acid (D), Glutamic Acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 20 5) Isoleucine (I), Leucine (L), Methionine (M), Alanine (A), Valine (V), and
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.*, *Science* 256: 1443-45 (1992). A “moderately conservative” replacement is any change having a nonnegative 25 value in the PAM250 log-likelihood matrix.

Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For 30 instance, GCG contains programs such as “Gap” and “Bestfit” which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of

organisms or between a wild type protein and a mutein thereof. *See, e.g.*, GCG Version

6.1. Other programs include FASTA, discussed *supra*.

A preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program

- 5 BLAST, especially blastp or tblastn. *See, e.g.*, Altschul *et al.*, *J. Mol. Biol.* 215: 403-410 (1990); Altschul *et al.*, *Nucleic Acids Res.* 25:3389-402 (1997). Preferred parameters for blastp are:

	Expectation value:	10 (default)
	Filter:	seg (default)
10	Cost to open a gap:	11 (default)
	Cost to extend a gap:	1 (default)
	Max. alignments:	100 (default)
	Word size:	11 (default)
	No. of descriptions:	100 (default)
15	Penalty Matrix:	BLOSUM62

The length of polypeptide sequences compared for homology will generally be at least about 16 amino acid residues, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. When searching a database containing sequences from a large number of 20 different organisms, it is preferable to compare amino acid sequences.

Algorithms other than blastp for database searching using amino acid sequences are known in the art. For instance, polypeptide sequences can be compared using FASTA, a program in GCG Version 6.1. FASTA (*e.g.*, FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the 25 query and search sequences (Pearson (1990), *supra*; Pearson (2000), *supra*). For example, percent sequence identity between amino acid sequences can be determined using FASTA with its default or recommended parameters (a word size of 2 and the PAM250 scoring matrix), as provided in GCG Version 6.1.

An “antibody” refers to an intact immunoglobulin, or to an antigen-binding portion 30 thereof that competes with the intact antibody for specific binding to a molecular species, *e.g.*, a polypeptide of the instant invention. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies.

Antigen-binding portions include, *inter alia*, Fab, Fab', F(ab')₂, Fv, dAb, and

complementarity determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide. A Fab fragment is a monovalent fragment consisting of the VL, VH, CL and CH1 domains; 5 a F(ab')₂ fragment is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consists of the VH and CH1 domains; a Fv fragment consists of the VL and VH domains of a single arm of an antibody; and a dAb fragment consists of a VH domain. *See, e.g., Ward et al., Nature 341: 544-546 (1989).*

By "bind specifically" and "specific binding" as used herein it is meant the ability 10 of the antibody to bind to a first molecular species in preference to binding to other molecular species with which the antibody and first molecular species are admixed. An antibody is said to "recognize" a first molecular species when it can bind specifically to that first molecular species.

A single-chain antibody (scFv) is an antibody in which VL and VH regions are 15 paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain. *See, e.g., Bird et al., Science 242: 423-426 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85: 5879-5883 (1988).* Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but 20 using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites. *See e.g., Holliger et al., Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993); Poljak et al., Structure 2: 1121-1123 (1994).* One or more CDRs 25 may be incorporated into a molecule either covalently or noncovalently to make it an immunoadhesin. An immunoadhesin may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the immunoadhesin to specifically bind to a particular antigen of interest. A chimeric antibody is an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies.

30 An antibody may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For instance, a naturally occurring immunoglobulin has two identical binding sites, a single-chain

antibody or Fab fragment has one binding site, while a “bispecific” or “bifunctional” antibody has two different binding sites.

- An “isolated antibody” is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. It is known that purified proteins, including purified antibodies, may be stabilized with non-naturally-associated components. The non-naturally-associated component may be a protein, such as albumin (e.g., BSA) or a chemical such as polyethylene glycol (PEG).
- 10 A “neutralizing antibody” or “an inhibitory antibody” is an antibody that inhibits the activity of a polypeptide or blocks the binding of a polypeptide to a ligand that normally binds to it. An “activating antibody” is an antibody that increases the activity of a polypeptide.

The term “epitope” includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is less than 1 μM , preferably less than 100 nM and most preferably less than 10 nM.

The term “patient” includes human and veterinary subjects.

Throughout this specification and claims, the word “comprise,” or variations such as “comprises” or “comprising,” will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

25 The term “breast specific” refers to a nucleic acid molecule or polypeptide that is expressed predominantly in the breast as compared to other tissues in the body. In a preferred embodiment, a “breast specific” nucleic acid molecule or polypeptide is detected at a level that is 1.5-fold higher than any other tissue in the body. In a more preferred embodiment, the “breast specific” nucleic acid molecule or polypeptide is detected at a 30 level that is 2-fold higher than any other tissue in the body, more preferably 5-fold higher, still more preferably at least 10-fold, 15-fold, 20-fold, 25-fold, 50-fold or 100-fold higher than any other tissue in the body. Nucleic acid molecule levels may be measured by nucleic acid hybridization, such as Northern blot hybridization, or quantitative PCR.

Polypeptide levels may be measured by any method known to accurately quantitate protein levels, such as Western blot analysis.

Nucleic Acid Molecules, Regulatory Sequences, Vectors, Host Cells and Recombinant Methods of Making Polypeptides

5 *Nucleic Acid Molecules*

One aspect of the invention provides isolated nucleic acid molecules that are specific to the breast or to breast cells or tissue or that are derived from such nucleic acid molecules. These isolated breast specific nucleic acids (BSNAs) may comprise cDNA genomic DNA, RNA, or a combination thereof, a fragment of one of these nucleic acids, 10 or may be a non-naturally occurring nucleic acid molecule. A BSNA may be derived from an animal. In a preferred embodiment, the BSNA is derived from a human or other mammal. In a more preferred embodiment, the BSNA is derived from a human or other primate. In an even more preferred embodiment, the BSNA is derived from a human.

In a preferred embodiment, the nucleic acid molecule encodes a polypeptide that 15 is specific to breast, a breast-specific polypeptide (BSP). In a more preferred embodiment, the nucleic acid molecule encodes a polypeptide that comprises an amino acid sequence of SEQ ID NO: 73-179. In another highly preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence of SEQ ID NO: 1-72. Nucleotide sequences of the instantly-described nucleic acid molecules were determined by assembling several DNA 20 molecules from either public or proprietary databases. Some of the underlying DNA sequences are the result, directly or indirectly, of at least one enzymatic polymerization reaction (*e.g.*, reverse transcription and/or polymerase chain reaction) using an automated sequencer (such as the MegaBACE™ 1000, Amersham Biosciences, Sunnyvale, CA, USA).

25 Nucleic acid molecules of the present invention may also comprise sequences that selectively hybridize to a nucleic acid molecule encoding a BSNA or a complement or antisense thereof. The hybridizing nucleic acid molecule may or may not encode a polypeptide or may or may not encode a BSP. However, in a preferred embodiment, the hybridizing nucleic acid molecule encodes a BSP. In a more preferred embodiment, the 30 invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule that encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 73-179. In an even more preferred

embodiment, the invention provides a nucleic acid molecule that selectively hybridizes to a nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 1-72 or the antisense sequence thereof. Preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a

5 BSP under low stringency conditions. More preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a BSP under moderate stringency conditions. Most preferably, the nucleic acid molecule selectively hybridizes to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a BSP under high stringency conditions. In

10 a preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule or the antisense sequence of a nucleic acid molecule encoding a polypeptide comprising an amino acid sequence of SEQ ID NO: 73-179. In a more preferred embodiment, the nucleic acid molecule hybridizes under low, moderate or high stringency conditions to a nucleic acid molecule or the antisense

15 sequence of a nucleic acid molecule comprising a nucleic acid sequence selected from SEQ ID NO: 1-72.

Nucleic acid molecules of the present invention may also comprise nucleic acid sequences that exhibit substantial sequence similarity to a nucleic acid encoding a BSP or a complement of the encoding nucleic acid molecule. In this embodiment, it is preferred

20 that the nucleic acid molecule exhibit substantial sequence similarity to a nucleic acid molecule encoding human BSP. More preferred is a nucleic acid molecule exhibiting substantial sequence similarity to a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 73-179. By substantial sequence similarity it is meant a nucleic acid molecule having at least 60%, more preferably at least 70%, even

25 more preferably at least 80% and even more preferably at least 85% sequence identity with a nucleic acid molecule encoding a BSP, such as a polypeptide having an amino acid sequence of SEQ ID NO: 73-179. In a more preferred embodiment, the similar nucleic acid molecule is one that has at least 90%, more preferably at least 95%, more preferably at least 97%, even more preferably at least 98%, and still more preferably at least 99%

30 sequence identity with a nucleic acid molecule encoding a BSP. Most preferred in this embodiment is a nucleic acid molecule that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a nucleic acid molecule encoding a BSP.

The nucleic acid molecules of the present invention are also inclusive of those exhibiting substantial sequence similarity to a BSNA or its complement. In this embodiment, it is preferred that the nucleic acid molecule exhibit substantial sequence similarity to a nucleic acid molecule having a nucleic acid sequence of SEQ ID NO: 1-72.

5 By substantial sequence similarity it is meant a nucleic acid molecule that has at least 60%, more preferably at least 70%, even more preferably at least 80% and even more preferably at least 85% sequence identity with a BSNA, such as one having a nucleic acid sequence of SEQ ID NO: 1-72. More preferred is a nucleic acid molecule that has at least 90%, more preferably at least 95%, more preferably at least 97%, even more preferably at 10 least 98%, and still more preferably at least 99% sequence identity with a BSNA. Most preferred is a nucleic acid molecule that has at least 99.5%, 99.6%, 99.7%, 99.8% or 99.9% sequence identity with a BSNA.

Nucleic acid molecules that exhibit substantial sequence similarity are inclusive of sequences that exhibit sequence identity over their entire length to a BSNA or to a nucleic acid molecule encoding a BSP, as well as sequences that are similar over only a part of its length. In this case, the part is at least 50 nucleotides of the BSNA or the nucleic acid molecule encoding a BSP, preferably at least 100 nucleotides, more preferably at least 150 or 200 nucleotides, even more preferably at least 250 or 300 nucleotides, still more preferably at least 400 or 500 nucleotides.

20 The substantially similar nucleic acid molecule may be a naturally occurring one that is derived from another species, especially one derived from another primate, wherein the similar nucleic acid molecule encodes an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 73-179 or demonstrates significant sequence identity to the nucleotide sequence of SEQ ID NO: 1-72. The similar nucleic acid 25 molecule may also be a naturally occurring nucleic acid molecule from a human, when the BSNA is a member of a gene family. The similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule derived from a non-primate, mammalian species, including without limitation, domesticated species, *e.g.*, dog, cat, mouse, rat, rabbit, hamster, cow, horse and pig; and wild animals, *e.g.*, monkey, fox, lions, tigers, 30 bears, giraffes, zebras, etc. The substantially similar nucleic acid molecule may also be a naturally occurring nucleic acid molecule derived from a non-mammalian species, such as birds or reptiles. The naturally occurring substantially similar nucleic acid molecule may be isolated directly from humans or other species. In another embodiment, the

substantially similar nucleic acid molecule may be one that is experimentally produced by random mutation of a nucleic acid molecule. In another embodiment, the substantially similar nucleic acid molecule may be one that is experimentally produced by directed mutation of a BSNA. In a preferred embodiment, the substantially similar nucleic acid
5 molecule is a BSNA.

The nucleic acid molecules of the present invention are also inclusive of allelic variants of a BSNA or a nucleic acid encoding a BSP. For example, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes and the sequence determined from one individual of a species may differ from other allelic forms present
10 within the population. More than 1.4 million SNPs have already been identified in the human genome, International Human Genome Sequencing Consortium, *Nature* 409: 860-921 (2001) – Variants with small deletions and insertions of more than a single nucleotide are also found in the general population, and often do not alter the function of the protein. In addition, amino acid substitutions occur frequently among natural allelic variants, and
15 often do not substantially change protein function.

In a preferred embodiment, the allelic variant is a variant of a gene, wherein the gene is transcribed into a mRNA that encodes a BSP. In a more preferred embodiment, the gene is transcribed into a mRNA that encodes a BSP comprising an amino acid sequence of SEQ ID NO: 73-179. In another preferred embodiment, the allelic variant is a
20 variant of a gene, wherein the gene is transcribed into a mRNA that is a BSNA. In a more preferred embodiment, the gene is transcribed into a mRNA that comprises the nucleic acid sequence of SEQ ID NO: 1-72. Also preferred is that the allelic variant be a naturally occurring allelic variant in the species of interest, particularly human.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid
25 sequences comprising a part of a nucleic acid sequence of the instant invention. The part may or may not encode a polypeptide, and may or may not encode a polypeptide that is a BSP. In a preferred embodiment, the part encodes a BSP. In one embodiment, the nucleic acid molecule comprises a part of a BSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that hybridizes or exhibits
30 substantial sequence similarity to a BSNA. In another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that is an allelic variant of a BSNA. In yet another embodiment, the nucleic acid molecule comprises a part of a nucleic acid molecule that encodes a BSP. A part comprises at least 10 nucleotides, more preferably at

least 15, 17, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400 or 500 nucleotides. The maximum size of a nucleic acid part is one nucleotide shorter than the sequence of the nucleic acid molecule encoding the full-length protein.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences that encode fusion proteins, homologous proteins, polypeptide fragments, mutoins and polypeptide analogs, as described *infra*.

Nucleic acid molecules of the present invention are also inclusive of nucleic acid sequences containing modifications of the native nucleic acid molecule. Examples of such modifications include, but are not limited to, nonnative internucleoside bonds, post-synthetic modifications or altered nucleotide analogues. One having ordinary skill in the art would recognize that the type of modification that may be made will depend upon the intended use of the nucleic acid molecule. For instance, when the nucleic acid molecule is used as a hybridization probe, the range of such modifications will be limited to those that permit sequence-discriminating base pairing of the resulting nucleic acid. When used to direct expression of RNA or protein *in vitro* or *in vivo*, the range of such modifications will be limited to those that permit the nucleic acid to function properly as a polymerization substrate. When the isolated nucleic acid is used as a therapeutic agent, the modifications will be limited to those that do not confer toxicity upon the isolated nucleic acid.

Accordingly, in one embodiment, a nucleic acid molecule may include nucleotide analogues that incorporate labels that are directly detectable, such as radiolabels or fluorophores, or nucleotide analogues that incorporate labels that can be visualized in a subsequent reaction, such as biotin or various haptens. The labeled nucleic acid molecules are particularly useful as hybridization probes.

Common radiolabeled analogues include those labeled with ^{33}P , ^{32}P , and ^{35}S , such as α - ^{32}P -dATP, α - ^{32}P -dCTP, α - ^{32}P -dGTP, α - ^{32}P -dTTP, α - ^{32}P -3'-dATP, α - ^{32}P -ATP, α - ^{32}P -CTP, α - ^{32}P -GTP, α - ^{32}P -UTP, α - ^{35}S -dATP, γ - ^{35}S -GTP, γ - ^{33}P -dATP, and the like.

Commercially available fluorescent nucleotide analogues readily incorporated into the nucleic acids of the present invention include Cy3-dCTP, Cy3-dUTP, Cy5-dCTP, Cy3-dUTP (Amersham Biosciences, Piscataway, New Jersey, USA), fluorescein-12-dUTP, tetramethylrhodamine-6-dUTP, Texas Red®-5-dUTP, Cascade Blue®-7-dUTP, BODIPY® FL-14-dUTP, BODIPY® TMR-14-dUTP, BODIPY® TR-14-dUTP, Rhodamine Green™-5-dUTP, Oregon Green® 488-5-dUTP, Texas Red®-12-dUTP,

BODIPY® 630/650-14-dUTP, BODIPY® 650/665-14-dUTP, Alexa Fluor® 488-5-dUTP, Alexa Fluor® 532-5-dUTP, Alexa Fluor® 568-5-dUTP, Alexa Fluor® 594-5-dUTP, Alexa Fluor® 546-14-dUTP, fluorescein-12-UTP, tetramethylrhodamine-6-UTP, Texas Red®-5-UTP, Cascade Blue®-7-UTP, BODIPY® FL-14-UTP, BODIPY® TMR-14-UTP,
5 BODIPY® TR-14-UTP, Rhodamine Green™-5-UTP, Alexa Fluor® 488-5-UTP, Alexa Fluor® 546-14-UTP (Molecular Probes, Inc. Eugene, OR, USA). One may also custom synthesize nucleotides having other fluorophores. *See Henegariu et al., Nature Biotechnol.* 18: 345-348 (2000).

Haptens that are commonly conjugated to nucleotides for subsequent labeling
10 include biotin (biotin-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA; biotin-21-UTP, biotin-21-dUTP, Clontech Laboratories, Inc., Palo Alto, CA, USA), digoxigenin (DIG-11-dUTP, alkali labile, DIG-11-UTP, Roche Diagnostics Corp., Indianapolis, IN, USA), and dinitrophenyl (dinitrophenyl-11-dUTP, Molecular Probes, Inc., Eugene, OR, USA).

15 Nucleic acid molecules of the present invention can be labeled by incorporation of labeled nucleotide analogues into the nucleic acid. Such analogues can be incorporated by enzymatic polymerization, such as by nick translation, random priming, polymerase chain reaction (PCR), terminal transferase tailing, and end-filling of overhangs, for DNA molecules, and *in vitro* transcription driven, e.g., from phage promoters, such as T7, T3,
20 and SP6, for RNA molecules. Commercial kits are readily available for each such labeling approach. Analogues can also be incorporated during automated solid phase chemical synthesis. Labels can also be incorporated after nucleic acid synthesis, with the 5' phosphate and 3' hydroxyl providing convenient sites for post-synthetic covalent attachment of detectable labels.

25 Other post-synthetic approaches also permit internal labeling of nucleic acids. For example, fluorophores can be attached using a cisplatin reagent that reacts with the N7 of guanine residues (and, to a lesser extent, adenine bases) in DNA, RNA, and Peptide Nucleic Acids (PNA) to provide a stable coordination complex between the nucleic acid and fluorophore label (Universal Linkage System) (available from Molecular Probes, Inc.,
30 Eugene, OR, USA and Amersham Pharmacia Biotech, Piscataway, NJ, USA); *see Alers et al., Genes, Chromosomes & Cancer* 25: 301- 305 (1999); Jelsma et al., *J. NIH Res.* 5: 82 (1994); Van Belkum et al., *BioTechniques* 16: 148-153 (1994). Alternatively, nucleic acids can be labeled using a disulfide-containing linker (FastTag™ Reagent, Vector

Laboratories, Inc., Burlingame, CA, USA) that is photo- or thermally coupled to the target nucleic acid using aryl azide chemistry; after reduction, a free thiol is available for coupling to a hapten, fluorophore, sugar, affinity ligand, or other marker.

One or more independent or interacting labels can be incorporated into the nucleic acid molecules of the present invention. For example, both a fluorophore and a moiety that in proximity thereto acts to quench fluorescence can be included to report specific hybridization through release of fluorescence quenching or to report exonucleotidic excision. *See, e.g.*, Tyagi *et al.*, *Nature Biotechnol.* 14: 303-308 (1996); Tyagi *et al.*, *Nature Biotechnol.* 16: 49-53 (1998); Sokol *et al.*, *Proc. Natl. Acad. Sci. USA* 95: 11538-11543 (1998); Kostrikis *et al.*, *Science* 279: 1228-1229 (1998); Marras *et al.*, *Genet. Anal.* 14: 151-156 (1999); Holland *et al.*, *Proc. Natl. Acad. Sci. USA* 88: 7276-7280 (1991); Heid *et al.*, *Genome Res.* 6(10): 986-94 (1996); Kuimelis *et al.*, *Nucleic Acids Symp. Ser.* (37): 255-6 (1997); and U.S. Patent Nos. 5,846,726, 5,925,517, 5,925,517, 5,723,591 and 5,538,848, the disclosures of which are incorporated herein by reference in their entireties.

Nucleic acid molecules of the present invention may also be modified by altering one or more native phosphodiester internucleoside bonds to more nuclease-resistant, internucleoside bonds. *See* Hartmann *et al.* (eds.), *Manual of Antisense Methodology: Perspectives in Antisense Science*, Kluwer Law International (1999); Stein *et al.* (eds.), *Applied Antisense Oligonucleotide Technology*, Wiley-Liss (1998); Chadwick *et al.* (eds.), *Oligonucleotides as Therapeutic Agents – Symposium No. 209*, John Wiley & Son Ltd (1997). Such altered internucleoside bonds are often desired for techniques or for targeted gene correction, Gamper *et al.*, *Nucl. Acids Res.* 28(21): 4332-4339 (2000). For double-stranded RNA inhibition which may utilize either natural ds RNA or ds RNA modified in its, sugar, phosphate or base, *see* Hannon, *Nature* 418(11): 244-251 (2002); Fire *et al.* in WO 99/32619; Tuschl *et al.* in US2002/0086356; Kruetzer *et al.* in WO 00/44895, the disclosures of which are incorporated herein by reference in their entirety. For circular antisense, see Kool in U.S. Patent No. 5,426,180, the disclosure of which is incorporated herein by reference in its entirety.

Modified oligonucleotide backbones include, without limitation, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including

- 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'.
- 5 Representative U.S. Patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050, the disclosures of which are incorporated herein by reference in their entireties. In a preferred embodiment, the modified internucleoside linkages may be used for antisense techniques.

Other modified oligonucleotide backbones do not include a phosphorus atom, but have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or 15 more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino 20 backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts. Representative U.S. patents that teach the preparation of the above backbones include, but are not limited to, U.S. Patent Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 25 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437 and 5,677,439; the disclosures of which are incorporated herein by reference in their entireties.

In other preferred nucleic acid molecules, both the sugar and the internucleoside linkage are replaced with novel groups, such as peptide nucleic acids (PNA). In PNA 30 compounds, the phosphodiester backbone of the nucleic acid is replaced with an amide-containing backbone, in particular by repeating N-(2-aminoethyl) glycine units linked by amide bonds. Nucleobases are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone, typically by methylene carbonyl linkages. PNA can be

synthesized using a modified peptide synthesis protocol. PNA oligomers can be synthesized by both Fmoc and tBoc methods. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference in its entirety. Automated PNA synthesis is readily achievable on commercial synthesizers (see, e.g., "PNA User's Guide," Rev. 2, February 1998, Perseptive Biosystems Part No. 60138, Applied Biosystems, Inc., Foster City, CA). PNA molecules are advantageous for a number of reasons. First, because the PNA backbone is uncharged, PNA/DNA and PNA/RNA duplexes have a higher thermal stability than is found in DNA/DNA and DNA/RNA duplexes. The Tm of a PNA/DNA or PNA/RNA duplex is generally 1°C higher per base pair than the Tm of the corresponding DNA/DNA or DNA/RNA duplex (in 100 mM NaCl). Second, PNA molecules can also form stable PNA/DNA complexes at low ionic strength, under conditions in which DNA/DNA duplex formation does not occur. Third, PNA also demonstrates greater specificity in binding to complementary DNA because a PNA/DNA mismatch is more destabilizing than DNA/DNA mismatch. A single mismatch in mixed a PNA/DNA 15-mer lowers the Tm by 8–20°C (15°C on average). In the corresponding DNA/DNA duplexes, a single mismatch lowers the Tm by 4–16°C (11°C on average). Because PNA probes can be significantly shorter than DNA probes, their specificity is greater. Fourth, PNA oligomers are resistant to degradation by enzymes, and the lifetime of these compounds is extended both *in vivo* and *in vitro* because nucleases and proteases do not recognize the PNA polyamide backbone with nucleobase sidechains. See, e.g., Ray *et al.*, *FASEB J.* 14(9): 1041-60 (2000); Nielsen *et al.*, *Pharmacol Toxicol.* 86(1): 3-7 (2000); Larsen *et al.*, *Biochim Biophys Acta.* 1489(1): 159-66 (1999); Nielsen, *Curr. Opin. Struct. Biol.* 9(3): 353-7 (1999), and Nielsen, *Curr. Opin. Biotechnol.* 10(1): 71-5 (1999).

Nucleic acid molecules may be modified compared to their native structure throughout the length of the nucleic acid molecule or can be localized to discrete portions thereof. As an example of the latter, chimeric nucleic acids can be synthesized that have discrete DNA and RNA domains and that can be used for targeted gene repair and modified PCR reactions, as further described in, Misra *et al.*, *Biochem.* 37: 1917-1925 (1998); and Finn *et al.*, *Nucl. Acids Res.* 24: 3357-3363 (1996), and U.S. Patent Nos. 5,760,012 and 5,731,181, the disclosures of which are incorporated herein by reference in their entireties.

Unless otherwise specified, nucleic acid molecules of the present invention can include any topological conformation appropriate to the desired use; the term thus explicitly comprehends, among others, single-stranded, double-stranded, triplexed, quadruplexed, partially double-stranded, partially-triplexed, partially-quadruplexed, 5 branched, hairpinned, circular, and padlocked conformations. Padlocked conformations and their utilities are further described in Banér *et al.*, *Curr. Opin. Biotechnol.* 12: 11-15 (2001); Escude *et al.*, *Proc. Natl. Acad. Sci. USA* 14: 96(19):10603-7 (1999); and Nilsson *et al.*, *Science* 265(5181): 2085-8 (1994). Triplexed and quadruplexed conformations, and their utilities, are reviewed in Praseuth *et al.*, *Biochim. Biophys. Acta.* 1489(1): 181-206 10 (1999); Fox, *Curr. Med. Chem.* 7(1): 17-37 (2000); Kochetkova *et al.*, *Methods Mol. Biol.* 130: 189-201 (2000); Chan *et al.*, *J. Mol. Med.* 75(4): 267-82 (1997); Rowley *et al.*, *Mol. Med.* 5(10): 693-700 (1999); Kool, *Annu Rev Biophys Biomol Struct.* 25: 1-28 (1996).

SNP Polymorphisms

Commonly, sequence differences between individuals involve differences in single 15 nucleotide positions. SNPs may account for 90% of human DNA polymorphism. Collins *et al.*, 8 *Genome Res.* 1229-31 (1998). SNPs include single base pair positions in genomic DNA at which different sequence alternatives (alleles) exist in a population. In addition, the least frequent allele generally must occur at a frequency of 1% or greater. DNA sequence variants with a reasonably high population frequency are observed 20 approximately every 1,000 nucleotide across the genome, with estimates as high as 1 SNP per 350 base pairs. Wang *et al.*, 280 *Science* 1077-82 (1998); Harding *et al.*, 60 *Am. J. Human Genet.* 772-89 (1997); Taillon-Miller *et al.*, 8 *Genome Res.* 748-54 (1998); Cargill *et al.*, 22 *Nat. Genet.* 231-38 (1999); and Semple *et al.*, 16 *Bioinform. Disc. Note* 735-38 25 (2000). The frequency of SNPs varies with the type and location of the change. In base substitutions, two-thirds of the substitutions involve the C-T and G-A type. This variation in frequency can be related to 5-methylcytosine deamination reactions that occur frequently, particularly at CpG dinucleotides. Regarding location, SNPs occur at a much higher frequency in non-coding regions than in coding regions. Information on over one million variable sequences is already publicly available via the Internet and more such 30 markers are available from commercial providers of genetic information. Kwok and Gu, 5 *Med. Today* 538-53 (1999).

Several definitions of SNPs exist. See, e.g., Brooks, 235 *Gene* 177-86 (1999). As used herein, the term "single nucleotide polymorphism" or "SNP" includes all single base variants, thus including nucleotide insertions and deletions in addition to single nucleotide substitutions. There are two types of nucleotide substitutions. A transition is the
5 replacement of one purine by another purine or one pyrimidine by another pyrimidine. A transversion is the replacement of a purine for a pyrimidine, or vice versa.

Numerous methods exist for detecting SNPs within a nucleotide sequence. A review of many of these methods can be found in Landegren *et al.*, 8 *Genome Res.* 769-76 (1998). For example, a SNP in a genomic sample can be detected by preparing a Reduced
10 Complexity Genome (RCG) from the genomic sample, then analyzing the RCG for the presence or absence of a SNP. See, e.g., WO 00/18960 which is herein incorporated by reference in its entirety. Multiple SNPs in a population of target polynucleotides in parallel can be detected using, for example, the methods of WO 00/50869 which is herein incorporated by reference in its entirety. Other SNP detection methods include the
15 methods of U.S. Pat. Nos. 6,297,018 and 6,322,980 which are herein incorporated by reference in their entirety. Furthermore, SNPs can be detected by restriction fragment length polymorphism (RFLP) analysis. See, e.g., U.S. Pat. Nos. 5,324,631; 5,645,995 which are herein incorporated by reference in their entirety. RFLP analysis of SNPs, however, is limited to cases where the SNP either creates or destroys a restriction enzyme
20 cleavage site. SNPs can also be detected by direct sequencing of the nucleotide sequence of interest. In addition, numerous assays based on hybridization have also been developed to detect SNPs and mismatch distinction by polymerases and ligases. Several web sites provide information about SNPs including Ensembl on the World Wide Web at ensemble.org, Sanger Institute on the World Wide Web at sanger.ac.uk/genetics/exon/,
25 National Center for Biotechnology Information (NCBI) on the World Wide Web at ncbi.nlm.nih.gov/SNP/ , The SNP Consortium Ltd. on the World Wide Web at.snp.cshl.org. The chromosomal locations for the compositions disclosed herein are provided below. In addition, one of ordinary skill in the art could use a BLAST against the genome or any of the databases cited above to find the chromosomal location.
30 Another a preferred method to find the genomic coordinates and associated SNPs would be to use the BLAT tool (genome.ucsc.edu, Kent et al. 2001, The Human Genome Browser at UCSC, Genome Research 996-1006 or Kent 2002 BLAT —The BLAST -Like

Alignment Tool Genome Research, 1-9). All web sites above were accessed December 3, 2003.

RNA interference

RNA interference refers to the process of sequence-specific post transcriptional gene silencing in animals mediated by short interfering RNAs (siRNA). Fire *et al.*, 1998, *Nature*, 391, 806. The corresponding process in plants is commonly referred to as post transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post transcriptional gene silencing is thought to be an evolutionarily conserved cellular defense mechanism used to prevent the expression of foreign genes which is commonly shared by diverse flora and phyla. Fire *et al.*, 1999, *Trends Genet.*, 15, 358. Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNA) derived from viral infection or the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response though a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA mediated activation of protein kinase PKR and 2',5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNA). Berstein *et al.*, 2001, *Nature*, 409, 363. Short interfering RNAs derived from dicer activity are typically about 21-23 nucleotides in length and comprise about 19 base pair duplexes. Dicer has also been implicated in the excision of 21 and 22 nucleotide small temporal RNAs (stRNA) from precursor RNA of conserved structure that are implicated in translational control. Hutvagner *et al.*, 2001, *Science*, 293, 834. The RNAi response also features an endonuclease complex containing a siRNA, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex. Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188.

Short interfering RNA mediated RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in C. Elegans. Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mouse embryos. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in Drosophila cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature*, 411, 494, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in Drosophila embryonic lysates (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21 nucleotide siRNA duplexes are most active when containing two nucleotide 3'-overhangs. Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with deoxy nucleotides (2'-H) was shown to be tolerated. Single mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end. Elbashir et al., 2001, *EMBO J.*, 20, 6877. Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA. Nykanen *et al.*, 2001, *Cell*, 107, 309.

Studies have shown that replacing the 3'-overhanging segments of a 21-mer siRNA duplex having 2 nucleotide 3' overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to 4 nucleotides on each end of the siRNA with deoxyribonucleotides has been reported to be well tolerated whereas complete substitution with deoxyribonucleotides results in no RNAi activity. Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877. In addition, Elbashir et al., supra, also report that substitution of siRNA with 2'-O-methyl nucleotides completely abolishes RNAi activity. Li *et al.*, WO 00/44914, and Beach *et al.*, WO 01/68836 both suggest that siRNA "may include modifications to either the phosphate-sugar back bone or the nucleoside to include at least one of a nitrogen or sulfur heteroatom", however neither application teaches to what extent these modifications are tolerated in siRNA molecules nor provide any examples of such modified siRNA. Kreutzer and Limmer, Canadian Patent Application No. 2,359,180, also

describe certain chemical modifications for use in dsRNA constructs in order to counteract activation of double-stranded RNA-dependent protein kinase PKR, specifically 2'-amino or 2'-O-methyl nucleotides, and nucleotides containing a 2'-O or 4'-C methylene bridge. However, Kreutzer and Limmer similarly fail to show to what extent these modifications 5 are tolerated in siRNA molecules nor do they provide any examples of such modified siRNA.

Parrish et al., 2000, *Molecular Cell*, 6, 1977-1087, tested certain chemical modifications targeting the unc-22 gene in *C. elegans* using long (>25 nt) siRNA transcripts. The authors describe the introduction of thiophosphate residues into these 10 siRNA transcripts by incorporating thiophosphate nucleotide analogs with T7 and T3 RNA polymerase and observed that "RNAs with two [phosphorothioate] modified bases also had substantial decreases in effectiveness as RNAi triggers; [phosphorothioate] modification of more than two residues greatly destabilized the RNAs in vitro and we were not able to assay interference activities." Parrish et al. at 1081. The authors also 15 tested certain modifications at the 2'-position of the nucleotide sugar in the long siRNA transcripts and observed that substituting deoxynucleotides for ribonucleotides "produced a substantial decrease in interference activity", especially in the case of Uridine to Thymidine and/or Cytidine to deoxy-Cytidine substitutions. Parrish et al. In addition, the authors tested certain base modifications, including substituting 4-thiouracil, 5- 20 bromouracil, 5-iodouracil, 3-(aminoallyl)uracil for uracil, and inosine for guanosine in sense and antisense strands of the siRNA, and found that whereas 4-thiouracil and 5- bromouracil were all well tolerated, inosine "produced a substantial decrease in 25 interference activity" when incorporated in either strand. Incorporation of 5-iodouracil and 3-(aminoallyl)uracil in the antisense strand resulted in substantial decrease in RNAi activity as well.

Beach et al., WO 01/68836, describes specific methods for attenuating gene expression using endogenously derived dsRNA. Tuschl et al., WO 01/75164, describes a Drosophila in vitro RNAi system and the use of specific siRNA molecules for certain functional genomic and certain therapeutic applications; although Tuschl, 2001, *Chem. Biochem.*, 2, 239-245, doubts that RNAi can be used to cure genetic diseases or viral infection due "to the danger of activating interferon response". Li et al., WO 00/44914, describes the use of specific dsRNAs for use in attenuating the expression of certain target

genes. Zernicka-Goetz et al., WO 01/36646, describes certain methods for inhibiting the expression of particular genes in mammalian cells using certain dsRNA molecules. Fire et al., WO 99/32619, U.S. Patent No. 6,506,559, the contents of which are hereby incorporated by reference in their entirety, describes particular methods for introducing 5 certain dsRNA molecules into cells for use in inhibiting gene expression. Plaetinck et al., WO 00/01846, describes certain methods for identifying specific genes responsible for conferring a particular phenotype in a cell using specific dsRNA molecules. Mello et al., WO 01/29058, describes the identification of specific genes involved in dsRNA mediated RNAi. Deschamps Depaillette et al., International PCT Publication No. WO 99/07409, 10 describes specific compositions consisting of particular dsRNA molecules combined with certain anti-viral agents. Driscoll et al., International PCT Publication No. WO 01/49844, describes specific DNA constructs for use in facilitating gene silencing in targeted organisms. Parrish et al., 2000, Molecular Cell, 6, 1977-1087, describes specific chemically modified siRNA constructs targeting the unc-22 gene of C. elegans. Tuschl et 15 al., International PCT Publication No. WO 02/44321, describe certain synthetic siRNA constructs.

Methods for Using Nucleic Acid Molecules as Probes and Primers

The isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize, and quantify hybridizing nucleic acids in, and 20 isolate hybridizing nucleic acids from, both genomic and transcript-derived nucleic acid samples. When free in solution, such probes are typically, but not invariably, detectably labeled; bound to a substrate, as in a microarray, such probes are typically, but not invariably unlabeled.

In one embodiment, the isolated nucleic acid molecules of the present invention 25 can be used as probes to detect and characterize gross alterations in the gene of a BSNA, such as deletions, insertions, translocations, and duplications of the BSNA genomic locus through fluorescence *in situ* hybridization (FISH) to chromosome spreads. *See, e.g.,* Andreeff et al. (eds.), Introduction to Fluorescence In Situ Hybridization: Principles and Clinical Applications, John Wiley & Sons (1999). The isolated nucleic acid molecules of 30 the present invention can be used as probes to assess smaller genomic alterations using, e.g., Southern blot detection of restriction fragment length polymorphisms. The isolated nucleic acid molecules of the present invention can be used as probes to isolate genomic

clones that include a nucleic acid molecule of the present invention, which thereafter can be restriction mapped and sequenced to identify deletions, insertions, translocations, and substitutions (single nucleotide polymorphisms, SNPs) at the sequence level.

Alternatively, detection techniques such as molecular beacons may be used, see Kostrikis
5 *et al. Science* 279:1228-1229 (1998).

The isolated nucleic acid molecules of the present invention can also be used as probes to detect, characterize, and quantify BSNA in, and isolate BSNA from, transcript-derived nucleic acid samples. In one embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by length,
10 and quantify mRNA by Northern blot of total or poly-A⁺- selected RNA samples. In another embodiment, the isolated nucleic acid molecules of the present invention can be used as hybridization probes to detect, characterize by location, and quantify mRNA by *in situ* hybridization to tissue sections. *See, e.g., Schwarchzacher et al., In Situ Hybridization*, Springer-Verlag New York (2000). In another preferred embodiment, the
15 isolated nucleic acid molecules of the present invention can be used as hybridization probes to measure the representation of clones in a cDNA library or to isolate hybridizing nucleic acid molecules acids from cDNA libraries, permitting sequence level characterization of mRNAs that hybridize to BSNA, including, without limitations, identification of deletions, insertions, substitutions, truncations, alternatively spliced forms
20 and single nucleotide polymorphisms. In yet another preferred embodiment, the nucleic acid molecules of the instant invention may be used in microarrays.

All of the aforementioned probe techniques are well within the skill in the art, and are described at greater length in standard texts such as Sambrook (2001), *supra*; Ausubel
25 (1999), *supra*; and Walker *et al.* (eds.), *The Nucleic Acids Protocols Handbook*, Humana Press (2000).

In another embodiment, a nucleic acid molecule of the invention may be used as a probe or primer to identify and/or amplify a second nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of the invention. In this embodiment, it is preferred that the probe or primer be derived from a nucleic acid molecule encoding a
30 BSP. More preferably, the probe or primer is derived from a nucleic acid molecule encoding a polypeptide having an amino acid sequence of SEQ ID NO: 73-179. Also preferred are probes or primers derived from a BSNA. More preferred are probes or

primers derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-72.

In general, a probe or primer is at least 10 nucleotides in length, more preferably at least 12, more preferably at least 14 and even more preferably at least 16 or 17 nucleotides 5 in length. In an even more preferred embodiment, the probe or primer is at least 18 nucleotides in length, even more preferably at least 20 nucleotides and even more preferably at least 22 nucleotides in length. Primers and probes may also be longer in length. For instance, a probe or primer may be 25 nucleotides in length, or may be 30, 40 or 50 nucleotides in length. Methods of performing nucleic acid hybridization using 10 oligonucleotide probes are well known in the art. See, e.g., Sambrook *et al.*, 1989, *supra*, Chapter 11 and pp. 11.31-11.32 and 11.40-11.44, which describes radiolabeling of short probes, and pp. 11.45-11.53, which describe hybridization conditions for oligonucleotide probes, including specific conditions for probe hybridization (pp. 11.50-11.51).

Methods of performing primer-directed amplification are also well known in the 15 art. Methods for performing the polymerase chain reaction (PCR) are compiled, *inter alia*, in McPherson, PCR Basics: From Background to Bench, Springer Verlag (2000); Innis *et al.* (eds.), PCR Applications: Protocols for Functional Genomics, Academic Press (1999); Gelfand *et al.* (eds.), PCR Strategies, Academic Press (1998); Newton *et al.*, PCR, Springer-Verlag New York (1997); Burke (ed.), PCR: Essential Techniques, John Wiley & Son Ltd (1996); White (ed.), PCR Cloning Protocols: From Molecular Cloning to 20 Genetic Engineering, Vol. 67, Humana Press (1996); and McPherson *et al.* (eds.), PCR 2: A Practical Approach, Oxford University Press, Inc. (1995). Methods for performing RT-PCR are collected, e.g., in Siebert *et al.* (eds.), Gene Cloning and Analysis by RT-PCR, Eaton Publishing Company/Bio Techniques Books Division, 1998; and Siebert (ed.), PCR 25 Technique:RT-PCR, Eaton Publishing Company/ BioTechniques Books (1995).

PCR and hybridization methods may be used to identify and/or isolate nucleic acid molecules of the present invention including allelic variants, homologous nucleic acid molecules and fragments. PCR and hybridization methods may also be used to identify, amplify and/or isolate nucleic acid molecules of the present invention that encode 30 homologous proteins, analogs, fusion proteins or muteins of the invention. Nucleic acid primers as described herein can be used to prime amplification of nucleic acid molecules of the invention, using transcript-derived or genomic DNA as the template.

These nucleic acid primers can also be used, for example, to prime single base extension (SBE) for SNP detection (*See, e.g.*, U.S. Pat. No. 6,004,744, the disclosure of which is incorporated herein by reference in its entirety).

Isothermal amplification approaches, such as rolling circle amplification, are also now well-described. *See, e.g.*, Schweitzer *et al.*, *Curr. Opin. Biotechnol.* 12(1): 21-7 (2001); International Patent publications WO 97/19193 and WO 00/15779, and U.S. Patent Nos. 5,854,033 and 5,714,320, the disclosures of which are incorporated herein by reference in their entireties. Rolling circle amplification can be combined with other techniques to facilitate SNP detection. *See, e.g.*, Lizardi *et al.*, *Nature Genet.* 19(3): 10 225-32 (1998).

Nucleic acid molecules of the present invention may be bound to a substrate either covalently or noncovalently. The substrate can be porous or solid, planar or non-planar, unitary or distributed. The bound nucleic acid molecules may be used as hybridization probes, and may be labeled or unlabeled. In a preferred embodiment, the bound nucleic acid molecules are unlabeled.

In one embodiment, the nucleic acid molecule of the present invention is bound to a porous substrate, *e.g.*, a membrane, typically comprising nitrocellulose, nylon, or positively charged derivatized nylon. The nucleic acid molecule of the present invention can be used to detect a hybridizing nucleic acid molecule that is present within a labeled nucleic acid sample, *e.g.*, a sample of transcript-derived nucleic acids. In another embodiment, the nucleic acid molecule is bound to a solid substrate, including, without limitation, glass, amorphous silicon, crystalline silicon or plastics. Examples of plastics include, without limitation, polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene, polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, nitrocellulose, or mixtures thereof. The solid substrate may be any shape, including rectangular, disk-like and spherical. In a preferred embodiment, the solid substrate is a microscope slide or slide-shaped substrate.

The nucleic acid molecule of the present invention can be attached covalently to a surface of the support substrate or applied to a derivatized surface in a chaotropic agent that facilitates denaturation and adherence by presumed noncovalent interactions, or some combination thereof. The nucleic acid molecule of the present invention can be bound to a substrate to which a plurality of other nucleic acids are concurrently bound, hybridization

to each of the plurality of bound nucleic acids being separately detectable. At low density, e.g. on a porous membrane, these substrate-bound collections are typically denominated macroarrays; at higher density, typically on a solid support, such as glass, these substrate bound collections of plural nucleic acids are colloquially termed microarrays. As used 5 herein, the term microarray includes arrays of all densities. It is, therefore, another aspect of the invention to provide microarrays that comprise one or more of the nucleic acid molecules of the present invention.

In yet another embodiment, the invention is directed to single exon probes based on the BSNAs disclosed herein.

10 *Expression Vectors, Host Cells and Recombinant Methods of Producing Polypeptides*

Another aspect of the present invention provides vectors that comprise one or more of the isolated nucleic acid molecules of the present invention, and host cells in which such vectors have been introduced.

15 The vectors can be used, *inter alia*, for propagating the nucleic acid molecules of the present invention in host cells (cloning vectors), for shuttling the nucleic acid molecules of the present invention between host cells derived from disparate organisms (shuttle vectors), for inserting the nucleic acid molecules of the present invention into host cell chromosomes (insertion vectors), for expressing sense or antisense RNA transcripts of 20 the nucleic acid molecules of the present invention *in vitro* or within a host cell, and for expressing polypeptides encoded by the nucleic acid molecules of the present invention, alone or as fusion proteins with heterologous polypeptides (expression vectors). Vectors are by now well known in the art, and are described, *inter alia*, in Jones *et al.* (eds.), Vectors: Cloning Applications: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Jones *et al.* (eds.), Vectors: Expression Systems: Essential Techniques (Essential Techniques Series), John Wiley & Son Ltd. (1998); Gacesa *et al.*, Vectors: Essential Data, John Wiley & Sons Ltd. (1995); Cid-Arregui (eds.), Viral Vectors: Basic Science and Gene Therapy, Eaton Publishing Co. (2000); Sambrook 25 (2001), *supra*; Ausubel (1999), *supra*. Furthermore, a variety of vectors are available 30 commercially. Use of existing vectors and modifications thereof are well within the skill in the art. Thus, only basic features need be described here.

Nucleic acid sequences may be expressed by operatively linking them to an expression control sequence in an appropriate expression vector and employing that expression vector to transform an appropriate unicellular host. Expression control sequences are sequences that control the transcription, post-transcriptional events and 5 translation of nucleic acid sequences. Such operative linking of a nucleic acid sequence of this invention to an expression control sequence, of course, includes, if not already part of the nucleic acid sequence, the provision of a translation initiation codon, ATG or GTG, in the correct reading frame upstream of the nucleic acid sequence.

A wide variety of host/expression vector combinations may be employed in 10 expressing the nucleic acid sequences of this invention. Useful expression vectors, for example, may consist of segments of chromosomal, non-chromosomal and synthetic nucleic acid sequences.

In one embodiment, prokaryotic cells may be used with an appropriate vector. Prokaryotic host cells are often used for cloning and expression. In a preferred 15 embodiment, prokaryotic host cells include *E. coli*, *Pseudomonas*, *Bacillus* and *Streptomyces*. In a preferred embodiment, bacterial host cells are used to express the nucleic acid molecules of the instant invention. Useful expression vectors for bacterial hosts include bacterial plasmids, such as those from *E. coli*, *Bacillus* or *Streptomyces*, including pBluescript, pGEX-2T, pUC vectors, col E1, pCR1, pBR322, pMB9 and their 20 derivatives, wider host range plasmids, such as RP4, phage DNAs, e.g., the numerous derivatives of phage lambda, e.g., NM989, λGT10 and λGT11, and other phages, e.g., M13 and filamentous single stranded phage DNA. Where *E. coli* is used as host, selectable markers are, analogously, chosen for selectivity in gram negative bacteria: e.g., typical markers confer resistance to antibiotics, such as ampicillin, tetracycline, 25 chloramphenicol, kanamycin, streptomycin and zeocin; auxotrophic markers can also be used.

In other embodiments, eukaryotic host cells, such as yeast, insect, mammalian or plant cells, may be used. Yeast cells, typically *S. cerevisiae*, are useful for eukaryotic 30 genetic studies, due to the ease of targeting genetic changes by homologous recombination and the ability to easily complement genetic defects using recombinantly expressed proteins. Yeast cells are useful for identifying interacting protein components, e.g. through use of a two-hybrid system. In a preferred embodiment, yeast cells are useful for protein expression. Vectors of the present invention for use in yeast will typically, but not

invariably, contain an origin of replication suitable for use in yeast and a selectable marker that is functional in yeast. Yeast vectors include Yeast Integrating plasmids (e.g., YIp5) and Yeast Replicating plasmids (the YRp and YE_p series plasmids), Yeast Centromere plasmids (the YCp series plasmids), Yeast Artificial Chromosomes (YACs) which are 5 based on yeast linear plasmids, denoted YLp, pGPD-2, 2μ plasmids and derivatives thereof, and improved shuttle vectors such as those described in Gietz *et al.*, *Gene*, 74: 15 527-34 (1988) (YIplac, YEplac and YCplac). Selectable markers in yeast vectors include a variety of auxotrophic markers, the most common of which are (in *Saccharomyces cerevisiae*) URA3, HIS3, LEU2, TRP1 and LYS2, which complement specific 10 auxotrophic mutations, such as ura3-52, his3-D1, leu2-D1, trp1-D1 and lys2-201.

Insect cells may be chosen for high efficiency protein expression. Where the host cells are from *Spodoptera frugiperda*, e.g., Sf9 and Sf21 cell lines, and expresSF™ cells (Protein Sciences Corp., Meriden, CT, USA), the vector replicative strategy is typically 15 based upon the baculovirus life cycle. Typically, baculovirus transfer vectors are used to replace the wild-type AcMNPV polyhedrin gene with a heterologous gene of interest. Sequences that flank the polyhedrin gene in the wild-type genome are positioned 5' and 3' of the expression cassette on the transfer vectors. Following co-transfection with 20 AcMNPV DNA, a homologous recombination event occurs between these sequences resulting in a recombinant virus carrying the gene of interest and the polyhedrin or p10 promoter. Selection can be based upon visual screening for lacZ fusion activity.

The host cells may also be mammalian cells, which are particularly useful for expression of proteins intended as pharmaceutical agents, and for screening of potential agonists and antagonists of a protein or a physiological pathway. Mammalian vectors intended for autonomous extrachromosomal replication will typically include a viral 25 origin, such as the SV40 origin (for replication in cell lines expressing the large T-antigen, such as COS1 and COS7 cells), the papillomavirus origin, or the EBV origin for long term episomal replication (for use, e.g., in 293-EBNA cells, which constitutively express the EBV EBNA-1 gene product and adenovirus E1A). Vectors intended for integration, and thus replication as part of the mammalian chromosome, can, but need not, include an 30 origin of replication functional in mammalian cells, such as the SV40 origin. Vectors based upon viruses, such as adenovirus, adeno-associated virus, vaccinia virus, and various mammalian retroviruses, will typically replicate according to the viral replicative strategy. Selectable markers for use in mammalian cells include, but are not limited to,

resistance to neomycin (G418), blasticidin, hygromycin and zeocin, and selection based upon the purine salvage pathway using HAT medium.

Expression in mammalian cells can be achieved using a variety of plasmids, including pSV2, pBC12BI, and p91023, as well as lytic virus vectors (*e.g.*, vaccinia virus, 5 adeno virus, and baculovirus), episomal virus vectors (*e.g.*, bovine papillomavirus), and retroviral vectors (*e.g.*, murine retroviruses). Useful vectors for insect cells include baculoviral vectors and pVL 941.

Plant cells can also be used for expression, with the vector replicon typically derived from a plant virus (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, 10 TMV) and selectable markers chosen for suitability in plants.

It is known that codon usage of different host cells may be different. For example, a plant cell and a human cell may exhibit a difference in codon preference for encoding a particular amino acid. As a result, human mRNA may not be efficiently translated in a plant, bacteria or insect host cell. Therefore, another embodiment of this invention is 15 directed to codon optimization. The codons of the nucleic acid molecules of the invention may be modified to resemble, as much as possible, genes naturally contained within the host cell without altering the amino acid sequence encoded by the nucleic acid molecule.

Any of a wide variety of expression control sequences may be used in these vectors to express the nucleic acid molecules of this invention. Such useful expression 20 control sequences include the expression control sequences associated with structural genes of the foregoing expression vectors. Expression control sequences that control transcription include, *e.g.*, promoters, enhancers and transcription termination sites. Expression control sequences in eukaryotic cells that control post-transcriptional events 25 include splice donor and acceptor sites and sequences that modify the half-life of the transcribed RNA, *e.g.*, sequences that direct poly(A) addition or binding sites for RNA-binding proteins. Expression control sequences that control translation include ribosome binding sites, sequences which direct targeted expression of the polypeptide to or within particular cellular compartments, and sequences in the 5' and 3' untranslated regions that modify the rate or efficiency of translation.

30 Examples of useful expression control sequences for a prokaryote, *e.g.*, *E. coli*, will include a promoter, often a phage promoter, such as phage lambda pL promoter, the trc promoter, a hybrid derived from the trp and lac promoters, the bacteriophage T7 promoter (in *E. coli* cells engineered to express the T7 polymerase), the TAC or TRC

system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, and the araBAD operon. Prokaryotic expression vectors may further include transcription terminators, such as the *aspA* terminator, and elements that facilitate translation, such as a consensus ribosome binding site and translation termination codon,

5 Schomer *et al.*, *Proc. Natl. Acad. Sci. USA* 83: 8506-8510 (1986).

Expression control sequences for yeast cells, typically *S. cerevisiae*, will include a yeast promoter, such as the CYC1 promoter, the GAL1 promoter, the GAL10 promoter, ADH1 promoter, the promoters of the yeast α -mating system, or the GPD promoter, and will typically have elements that facilitate transcription termination, such as the

10 transcription termination signals from the CYC1 or ADH1 gene.

Expression vectors useful for expressing proteins in mammalian cells will include a promoter active in mammalian cells. These promoters include, but are not limited to, those derived from mammalian viruses, such as the enhancer-promoter sequences from the immediate early gene of the human cytomegalovirus (CMV), the enhancer-promoter sequences from the Rous sarcoma virus long terminal repeat (RSV LTR), the enhancer-promoter from SV40 and the early and late promoters of adenovirus. Other expression control sequences include the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase. Other expression control sequences include those from the gene comprising the BSNA of interest. Often, expression is enhanced by incorporation of polyadenylation sites, such as the late SV40 polyadenylation site and the polyadenylation signal and transcription termination sequences from the bovine growth hormone (BGH) gene, and ribosome binding sites. Furthermore, vectors can include introns, such as intron II of rabbit β -globin gene and the SV40 splice elements.

Preferred nucleic acid vectors also include a selectable or amplifiable marker gene 25 and means for amplifying the copy number of the gene of interest. Such marker genes are well known in the art. Nucleic acid vectors may also comprise stabilizing sequences (*e.g.*, ori- or ARS-like sequences and telomere-like sequences), or may alternatively be designed to favor directed or non-directed integration into the host cell genome. In a preferred embodiment, nucleic acid sequences of this invention are inserted in frame into an 30 expression vector that allows a high level expression of an RNA which encodes a protein comprising the encoded nucleic acid sequence of interest. Nucleic acid cloning and sequencing methods are well known to those of skill in the art and are described in an assortment of laboratory manuals, including Sambrook (1989), *supra*, Sambrook (2000),

supra; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. Product information from manufacturers of biological, chemical and immunological reagents also provide useful information.

Expression vectors may be either constitutive or inducible. Inducible vectors 5 include either naturally inducible promoters, such as the trc promoter, which is regulated by the lac operon, and the pL promoter, which is regulated by tryptophan, the MMTV-LTR promoter, which is inducible by dexamethasone, or can contain synthetic promoters and/or additional elements that confer inducible control on adjacent promoters. Examples of inducible synthetic promoters are the hybrid Plac/ara-1 promoter and the 10 PLtetO-1 promoter. The PLtetO-1 promoter takes advantage of the high expression levels from the PL promoter of phage lambda, but replaces the lambda repressor sites with two copies of operator 2 of the Tn10 tetracycline resistance operon, causing this promoter to be tightly repressed by the Tet repressor protein and induced in response to tetracycline (Tc) and Tc derivatives such as anhydrotetracycline. Vectors may also be inducible 15 because they contain hormone response elements, such as the glucocorticoid response element (GRE) and the estrogen response element (ERE), which can confer hormone inducibility where vectors are used for expression in cells having the respective hormone receptors. To reduce background levels of expression, elements responsive to ecdysone, an insect hormone, can be used instead, with coexpression of the ecdysone receptor.

20 In one embodiment of the invention, expression vectors can be designed to fuse the expressed polypeptide to small protein tags that facilitate purification and/or visualization. Such tags include a polyhistidine tag that facilitates purification of the fusion protein by immobilized metal affinity chromatography, for example using NiNTA resin (Qiagen Inc., Valencia, CA, USA) or TALONTM resin (cobalt immobilized affinity chromatography 25 medium, Clontech Labs, Palo Alto, CA, USA). The fusion protein can include a chitin-binding tag and self-excising intein, permitting chitin-based purification with self-removal of the fused tag (IMPACTTM system, New England Biolabs, Inc., Beverley, MA, USA). Alternatively, the fusion protein can include a calmodulin-binding peptide tag, permitting 30 purification by calmodulin affinity resin (Stratagene, La Jolla, CA, USA), or a specifically excisable fragment of the biotin carboxylase carrier protein, permitting purification of *in vivo* biotinylated protein using an avidin resin and subsequent tag removal (Promega, Madison, WI, USA). As another useful alternative, the polypeptides of the present invention can be expressed as a fusion to glutathione-S-transferase, the affinity and

specificity of binding to glutathione permitting purification using glutathione affinity resins, such as Glutathione-Superflow Resin (Clontech Laboratories, Palo Alto, CA, USA), with subsequent elution with free glutathione. Other tags include, for example, the Xpress epitope, detectable by anti-Xpress antibody (Invitrogen, Carlsbad, CA, USA), a

- 5 myc tag, detectable by anti-myc tag antibody, the V5 epitope, detectable by anti-V5 antibody (Invitrogen, Carlsbad, CA, USA), FLAG® epitope, detectable by anti-FLAG® antibody (Stratagene, La Jolla, CA, USA), and the HA epitope, detectable by anti-HA antibody.

For secretion of expressed polypeptides, vectors can include appropriate sequences
10 that encode secretion signals, such as leader peptides. For example, the pSecTag2 vectors (Invitrogen, Carlsbad, CA, USA) are 5.2 kb mammalian expression vectors that carry the secretion signal from the V-J2-C region of the mouse Ig kappa-chain for efficient secretion of recombinant proteins from a variety of mammalian cell lines.

Expression vectors can also be designed to fuse proteins encoded by the
15 heterologous nucleic acid insert to polypeptides that are larger than purification and/or identification tags. Useful protein fusions include those that permit display of the encoded protein on the surface of a phage or cell, fusions to intrinsically fluorescent proteins, such as those that have a green fluorescent protein (GFP)-like chromophore, fusions to the IgG Fc region, and fusions for use in two hybrid systems.

20 Vectors for phage display fuse the encoded polypeptide to, *e.g.*, the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13. *See Barbas et al., Phage Display: A Laboratory Manual*, Cold Spring Harbor Laboratory Press (2001); Kay *et al.* (eds.), *Phage Display of Peptides and Proteins: A Laboratory Manual*, Academic Press, Inc., (1996); Abelson *et al.* (eds.), *Combinatorial Chemistry* (*Methods in Enzymology*, Vol. 267) Academic Press (1996). Vectors for yeast display, *e.g.* the pYD1 yeast display vector (Invitrogen, Carlsbad, CA, USA), use the α-agglutinin yeast adhesion receptor to display recombinant protein on the surface of *S. cerevisiae*. Vectors for mammalian display, *e.g.*, the pDisplay™ vector (Invitrogen, Carlsbad, CA, USA), target recombinant proteins using an N-terminal cell surface targeting signal and a C-terminal transmembrane anchoring domain of platelet derived growth factor receptor.

30 A wide variety of vectors now exist that fuse proteins encoded by heterologous nucleic acids to the chromophore of the substrate-independent, intrinsically fluorescent

green fluorescent protein from *Aequorea victoria* (“GFP”) and its variants. The GFP-like chromophore can be selected from GFP-like chromophores found in naturally occurring proteins, such as *A. victoria* GFP (GenBank accession number AAA27721), *Renilla reniformis* GFP, FP583 (GenBank accession no. AF168419) (DsRed), FP593 (AF272711),
5 FP483 (AF168420), FP484 (AF168424), FP595 (AF246709), FP486 (AF168421), FP538 (AF168423), and FP506 (AF168422), and need include only so much of the native protein as is needed to retain the chromophore’s intrinsic fluorescence. Methods for determining the minimal domain required for fluorescence are known in the art. See Li *et al.*, *J. Biol. Chem.* 272: 28545-28549 (1997). Alternatively, the GFP-like chromophore can be
10 selected from GFP-like chromophores modified from those found in nature. The methods for engineering such modified GFP-like chromophores and testing them for fluorescence activity, both alone and as part of protein fusions, are well known in the art. See Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Palm *et al.*, *Methods Enzymol.* 302: 378-394 (1999). A variety of such modified chromophores are now commercially available and can readily
15 be used in the fusion proteins of the present invention. These include EGFP (“enhanced GFP”), EBFP (“enhanced blue fluorescent protein”), BFP2, EYFP (“enhanced yellow fluorescent protein”), ECFP (“enhanced cyan fluorescent protein”) or Citrine. EGFP (see, e.g., Cormack *et al.*, *Gene* 173: 33-38 (1996); U.S. Patent Nos. 6,090,919 and 5,804,387, the disclosures of which are incorporated herein by reference in their entireties) is found
20 on a variety of vectors, both plasmid and viral, which are available commercially (Clontech Labs, Palo Alto, CA, USA); EBFP is optimized for expression in mammalian cells whereas BFP2, which retains the original jellyfish codons, can be expressed in bacteria (see, e.g., Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996) and Cormack *et al.*, *Gene* 173: 33-38 (1996)). Vectors containing these blue-shifted variants are available from
25 Clontech Labs (Palo Alto, CA, USA). Vectors containing EYFP, ECFP (see, e.g., Heim *et al.*, *Curr. Biol.* 6: 178-182 (1996); Miyawaki *et al.*, *Nature* 388: 882-887 (1997)) and Citrine (see, e.g., Heikal *et al.*, *Proc. Natl. Acad. Sci. USA* 97: 11996-12001 (2000)) are also available from Clontech Labs. The GFP-like chromophore can also be drawn from other modified GFPs, including those described in U.S. Patent Nos. 6,124,128; 6,096,865;
30 6,090,919; 6,066,476; 6,054,321; 6,027,881; 5,968,750; 5,874,304; 5,804,387; 5,777,079; 5,741,668; and 5,625,048, the disclosures of which are incorporated herein by reference in their entireties. See also Conn (ed.), Green Fluorescent Protein (Methods in Enzymology, Vol. 302), Academic Press, Inc. (1999); Yang, *et al.*, *J Biol Chem*, 273: 8212-6 (1998);

Bevis *et al.*, *Nature Biotechnology*, 20:83-7 (2002). The GFP-like chromophore of each of these GFP variants can usefully be included in the fusion proteins of the present invention.

Fusions to the IgG Fc region increase serum half-life of protein pharmaceutical products through interaction with the FcRn receptor (also denominated the FcRp receptor and the Brambell receptor, FcRb), further described in International Patent Application Nos. WO 97/43316, WO 97/34631, WO 96/32478, and WO 96/18412, the disclosures of which are incorporated herein by reference in their entireties.

For long-term, high-yield recombinant production of the polypeptides of the present invention, stable expression is preferred. Stable expression is readily achieved by integration into the host cell genome of vectors having selectable markers, followed by selection of these integrants. Vectors such as pUB6/V5-His A, B, and C (Invitrogen, Carlsbad, CA, USA) are designed for high-level stable expression of heterologous proteins in a wide range of mammalian tissue types and cell lines. pUB6/V5-His uses the promoter/enhancer sequence from the human ubiquitin C gene to drive expression of recombinant proteins: expression levels in 293, CHO, and NIH3T3 cells are comparable to levels from the CMV and human EF-1 α promoters. The bsd gene permits rapid selection of stably transfected mammalian cells with the potent antibiotic blasticidin.

Replication incompetent retroviral vectors, typically derived from Moloney murine leukemia virus, also are useful for creating stable transfectants having integrated provirus. The highly efficient transduction machinery of retroviruses, coupled with the availability of a variety of packaging cell lines such as RetroPackTM PT 67, EcoPack2TM-293, AmphiPack-293, and GP2-293 cell lines (all available from Clontech Laboratories, Palo Alto, CA, USA) allow a wide host range to be infected with high efficiency; varying the multiplicity of infection readily adjusts the copy number of the integrated provirus.

Of course, not all vectors and expression control sequences will function equally well to express the nucleic acid molecules of this invention. Neither will all hosts function equally well with the same expression system. However, one of skill in the art may make a selection among these vectors, expression control sequences and hosts without undue experimentation and without departing from the scope of this invention. For example, in selecting a vector, the host must be considered because the vector must be replicated in it. The vector's copy number, the ability to control that copy number, the ability to control integration, if any, and the expression of any other proteins encoded by the vector, such as

- an antibiotic or other selection marker, should also be considered. The present invention further includes host cells comprising the vectors of the present invention, either present episomally within the cell or integrated, in whole or in part, into the host cell chromosome. Among other considerations, some of which are described above, a host cell strain may be
- 5 chosen for its ability to process the expressed polypeptide in the desired fashion. Such post-translational modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation, and it is an aspect of the present invention to provide BSPs with such post-translational modifications.
- 10 In selecting an expression control sequence, a variety of factors should also be considered. These include, for example, the relative strength of the sequence, its controllability, and its compatibility with the nucleic acid molecules of this invention, particularly with regard to potential secondary structures. Unicellular hosts should be selected by consideration of their compatibility with the chosen vector, the toxicity of the
- 15 product coded for by the nucleic acid sequences of this invention, their secretion characteristics, their ability to fold the polypeptide correctly, their fermentation or culture requirements, and the ease of purification from them of the products coded for by the nucleic acid molecules of this invention.
- The recombinant nucleic acid molecules and more particularly, the expression vectors of this invention may be used to express the polypeptides of this invention as recombinant polypeptides in a heterologous host cell. The polypeptides of this invention may be full-length or less than full-length polypeptide fragments recombinantly expressed from the nucleic acid molecules according to this invention. Such polypeptides include analogs, derivatives and muteins that may or may not have biological activity.
- 20 Vectors of the present invention will also often include elements that permit *in vitro* transcription of RNA from the inserted heterologous nucleic acid. Such vectors typically include a phage promoter, such as that from T7, T3, or SP6, flanking the nucleic acid insert. Often two different such promoters flank the inserted nucleic acid, permitting separate *in vitro* production of both sense and antisense strands.
- 25 Transformation and other methods of introducing nucleic acids into a host cell (e.g., conjugation, protoplast transformation or fusion, transfection, electroporation, liposome delivery, membrane fusion techniques, high velocity DNA-coated pellets, viral infection and protoplast fusion) can be accomplished by a variety of methods which are

well known in the art (See, for instance, Ausubel, *supra*, and Sambrook *et al.*, *supra*). Bacterial, yeast, plant or mammalian cells are transformed or transfected with an expression vector, such as a plasmid, a cosmid, or the like, wherein the expression vector comprises the nucleic acid of interest. Alternatively, the cells may be infected by a viral expression vector comprising the nucleic acid of interest. Depending upon the host cell, vector, and method of transformation used, transient or stable expression of the polypeptide will be constitutive or inducible. One having ordinary skill in the art will be able to decide whether to express a polypeptide transiently or stably, and whether to express the protein constitutively or inducibly.

- 10 A wide variety of unicellular host cells are useful in expressing the DNA sequences of this invention. These hosts may include well known eukaryotic and prokaryotic hosts, such as strains of, fungi, yeast, insect cells such as *Spodoptera frugiperda* (SF9), animal cells such as CHO, as well as plant cells in tissue culture. Representative examples of appropriate host cells include, but are not limited to, bacterial
- 15 cells, such as *E. coli*, *Caulobacter crescentus*, *Streptomyces* species, and *Salmonella typhimurium*; yeast cells, such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Pichia pastoris*, *Pichia methanolica*; insect cell lines, such as those from *Spodoptera frugiperda*, e.g., Sf9 and Sf21 cell lines, and expresSF™ cells (Protein Sciences Corp., Meriden, CT, USA), *Drosophila* S2 cells, and *Trichoplusia ni* High Five® Cells
- 20 (Invitrogen, Carlsbad, CA, USA); and mammalian cells. Typical mammalian cells include BHK cells, BSC 1 cells, BSC 40 cells, BMT 10 cells, VERO cells, COS1 cells, COS7 cells, Chinese hamster ovary (CHO) cells, 3T3 cells, NIH 3T3 cells, 293 cells, HEPG2 cells, HeLa cells, L cells, MDCK cells, HEK293 cells, WI38 cells, murine ES cell lines (e.g., from strains 129/SV, C57/BL6, DBA-1, 129/SVJ), K562 cells, Jurkat cells, and
- 25 BW5147 cells. Other mammalian cell lines are well known and readily available from the American Type Culture Collection (ATCC) (Manassas, VA, USA) and the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository at the Coriell Cell Repositories (Camden, NJ, USA). Cells or cell lines derived from breast are particularly preferred because they may provide a more native post-translational
- 30 processing. Particularly preferred are human breast cells.

Particular details of the transfection, expression and purification of recombinant proteins are well documented and are understood by those of skill in the art. Further details on the various technical aspects of each of the steps used in recombinant

production of foreign genes in bacterial cell expression systems can be found in a number of texts and laboratory manuals in the art. See, e.g., Ausubel (1992), *supra*, Ausubel (1999), *supra*, Sambrook (1989), *supra*, and Sambrook (2001), *supra*.

Methods for introducing the vectors and nucleic acid molecules of the present invention into the host cells are well known in the art; the choice of technique will depend primarily upon the specific vector to be introduced and the host cell chosen.

Nucleic acid molecules and vectors may be introduced into prokaryotes, such as *E. coli*, in a number of ways. For instance, phage lambda vectors will typically be packaged using a packaging extract (e.g., Gigapack® packaging extract, Stratagene, La Jolla, CA, USA), and the packaged virus used to infect *E. coli*.

Plasmid vectors will typically be introduced into chemically competent or electrocompetent bacterial cells. *E. coli* cells can be rendered chemically competent by treatment, e.g., with CaCl₂, or a solution of Mg²⁺, Mn²⁺, Ca²⁺, Rb⁺ or K⁺, dimethyl sulfoxide, dithiothreitol, and hexamine cobalt (III), Hanahan, *J. Mol. Biol.* 166(4):557-80 (1983), and vectors introduced by heat shock. A wide variety of chemically competent strains are also available commercially (e.g., Epicurian Coli® XL10-Gold® Ultracompetent Cells (Stratagene, La Jolla, CA, USA); DH5 α competent cells (Clontech Laboratories, Palo Alto, CA, USA); and TOP10 Chemically Competent *E. coli* Kit (Invitrogen, Carlsbad, CA, USA)). Bacterial cells can be rendered electrocompetent to take up exogenous DNA by electroporation by various pre-pulse treatments; vectors are introduced by electroporation followed by subsequent outgrowth in selected media. An extensive series of protocols is provided by BioRad (Richmond, CA, USA).

Vectors can be introduced into yeast cells by spheroplasting, treatment with lithium salts, electroporation, or protoplast fusion. Spheroplasts are prepared by the action of hydrolytic enzymes such as a snail-gut extract, usually denoted Glusulase or Zymolyase, or an enzyme from *Arthrobacter luteus* to remove portions of the cell wall in the presence of osmotic stabilizers, typically 1 M sorbitol. DNA is added to the spheroplasts, and the mixture is co-precipitated with a solution of polyethylene glycol (PEG) and Ca²⁺. Subsequently, the cells are resuspended in a solution of sorbitol, mixed with molten agar and then layered on the surface of a selective plate containing sorbitol.

For lithium-mediated transformation, yeast cells are treated with lithium acetate to permeabilize the cell wall, DNA is added and the cells are co-precipitated with PEG. The cells are exposed to a brief heat shock, washed free of PEG and lithium acetate, and

subsequently spread on plates containing ordinary selective medium. Increased frequencies of transformation are obtained by using specially-prepared single-stranded carrier DNA and certain organic solvents. Schiestl *et al.*, *Curr. Genet.* 16(5-6): 339-46 (1989).

5 For electroporation, freshly-grown yeast cultures are typically washed, suspended in an osmotic protectant, such as sorbitol, mixed with DNA, and the cell suspension pulsed in an electroporation device. Subsequently, the cells are spread on the surface of plates containing selective media. Becker *et al.*, *Methods Enzymol.* 194: 182-187 (1991). The efficiency of transformation by electroporation can be increased over 100-fold by
10 using PEG, single-stranded carrier DNA and cells that are in late log-phase of growth. Larger constructs, such as YACs, can be introduced by protoplast fusion.

Mammalian and insect cells can be directly infected by packaged viral vectors, or transfected by chemical or electrical means. For chemical transfection, DNA can be coprecipitated with CaPO₄ or introduced using liposomal and nonliposomal lipid-based
15 agents. Commercial kits are available for CaPO₄ transfection (CalPhos™ Mammalian Transfection Kit, Clontech Laboratories, Palo Alto, CA, USA), and lipid-mediated transfection can be practiced using commercial reagents, such as LIPOFECTAMINE™ 2000, LIPOFECTAMINE™ Reagent, CELLFECTIN® Reagent, and LIPOFECTIN® Reagent (Invitrogen, Carlsbad, CA, USA), DOTAP Liposomal Transfection Reagent,
20 FuGENE 6, X-tremeGENE Q2, DOSPER, (Roche Molecular Biochemicals, Indianapolis, IN USA), Effectene™, PolyFect®, Superfect® (Qiagen, Inc., Valencia, CA, USA). Protocols for electroporating mammalian cells can be found in, for example, ; Norton *et al.* (eds.), *Gene Transfer Methods: Introducing DNA into Living Cells and Organisms*, BioTechniques Books, Eaton Publishing Co. (2000). Other transfection techniques
25 include transfection by particle bombardment and microinjection. See, e.g., Cheng *et al.*, *Proc. Natl. Acad. Sci. USA* 90(10): 4455-9 (1993); Yang *et al.*, *Proc. Natl. Acad. Sci. USA* 87(24): 9568-72 (1990).

Production of the recombinantly produced proteins of the present invention can optionally be followed by purification.

30 Purification of recombinantly expressed proteins is now well within the skill in the art and thus need not be detailed here. See, e.g., Thorner *et al.* (eds.), *Applications of Chimeric Genes and Hybrid Proteins, Part A: Gene Expression and Protein Purification* (Methods in Enzymology, Vol. 326), Academic Press (2000); Harbin (ed.), *Cloning, Gene*

Expression and Protein Purification : Experimental Procedures and Process Rationale, Oxford Univ. Press (2001); Marshak *et al.*, Strategies for Protein Purification and Characterization: A Laboratory Course Manual, Cold Spring Harbor Laboratory Press (1996); and Roe (ed.), Protein Purification Applications, Oxford University Press (2001).

5 Briefly, however, if purification tags have been fused through use of an expression vector that appends such tag, purification can be effected, at least in part, by means appropriate to the tags, such as use of immobilized metal affinity chromatography for polyhistidine tags. Other techniques common in the art include ammonium sulfate fractionation, immunoprecipitation, fast protein liquid chromatography (FPLC), high
10 performance liquid chromatography (HPLC), and preparative gel electrophoresis.

Polypeptides, including Fragments Muteins, Homologous Proteins, Allelic Variants, Analogs and Derivatives

Another aspect of the invention relates to polypeptides encoded by the nucleic acid molecules described herein. In a preferred embodiment, the polypeptide is a breast
15 specific polypeptide (BSP). In an even more preferred embodiment, the polypeptide comprises an amino acid sequence of SEQ ID NO:73-179 or is derived from a polypeptide having the amino acid sequence of SEQ ID NO: 73-179. A polypeptide as defined herein may be produced recombinantly, as discussed *supra*, may be isolated from a cell that naturally expresses the protein, or may be chemically synthesized following the teachings
20 of the specification and using methods well known to those having ordinary skill in the art.

Polypeptides of the present invention may also comprise a part or fragment of a BSP. In a preferred embodiment, the fragment is derived from a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 73-179.

Polypeptides of the present invention comprising a part or fragment of an entire BSP may or may not be BSPs. For example, a full-length polypeptide may be breast-specific, while a fragment thereof may be found in other tissues as well as in breast. A polypeptide that is not a BSP, whether it is a fragment, analog, mutein, homologous protein or derivative, is nevertheless useful, especially for immunizing animals to prepare anti-BSP antibodies. In a preferred embodiment, the part or fragment is a BSP. Methods of determining whether a
30 polypeptide of the present invention is a BSP are described *infra*.

Polypeptides of the present invention comprising fragments of at least 6 contiguous amino acids are also useful in mapping B cell and T cell epitopes of the

reference protein. *See, e.g.*, Geysen *et al.*, *Proc. Natl. Acad. Sci. USA* 81: 3998-4002 (1984) and U.S. Patent Nos. 4,708,871 and 5,595,915, the disclosures of which are incorporated herein by reference in their entireties. Because the fragment need not itself be immunogenic, part of an immunodominant epitope, nor even recognized by native antibody, to be useful in such epitope mapping, all fragments of at least 6 amino acids of a polypeptide of the present invention have utility in such a study.

Polypeptides of the present invention comprising fragments of at least 8 contiguous amino acids, often at least 15 contiguous amino acids, are useful as immunogens for raising antibodies that recognize polypeptides of the present invention.

10 *See, e.g.*, Lerner, *Nature* 299: 592-596 (1982); Shinnick *et al.*, *Annu. Rev. Microbiol.* 37: 425-46 (1983); Sutcliffe *et al.*, *Science* 219: 660-6 (1983). As further described in the above-cited references, virtually all 8-mers, conjugated to a carrier, such as a protein, prove immunogenic and are capable of eliciting antibody for the conjugated peptide; accordingly, all fragments of at least 8 amino acids of the polypeptides of the present invention have utility as immunogens.

Polypeptides comprising fragments of at least 8, 9, 10 or 12 contiguous amino acids are also useful as competitive inhibitors of binding of the entire polypeptide, or a portion thereof, to antibodies (as in epitope mapping), and to natural binding partners, such as subunits in a multimeric complex or to receptors or ligands of the subject protein;

20 this competitive inhibition permits identification and separation of molecules that bind specifically to the polypeptide of interest. See U.S. Patent Nos. 5,539,084 and 5,783,674, incorporated herein by reference in their entireties.

The polypeptide of the present invention thus preferably is at least 6 amino acids in length, typically at least 8, 9, 10 or 12 amino acids in length, and often at least 15 amino acids in length. Often, the polypeptide of the present invention is at least 20 amino acids in length, even 25 amino acids, 30 amino acids, 35 amino acids, or 50 amino acids or more in length. Of course, larger polypeptides having at least 75 amino acids, 100 amino acids, or even 150 amino acids are also useful, and at times preferred.

One having ordinary skill in the art can produce fragments by truncating the nucleic acid molecule, *e.g.*, a BSNA, encoding the polypeptide and then expressing it recombinantly. Alternatively, one can produce a fragment by chemically synthesizing a portion of the full-length polypeptide. One may also produce a fragment by enzymatically cleaving either a recombinant polypeptide or an isolated naturally occurring polypeptide.

Methods of producing polypeptide fragments are well known in the art. *See, e.g.,* Sambrook (1989), *supra*; Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. In one embodiment, a polypeptide comprising only a fragment, preferably a fragment of a BSP, may be produced by chemical or enzymatic cleavage of a BSP

- 5 polypeptide. In a preferred embodiment, a polypeptide fragment is produced by expressing a nucleic acid molecule of the present invention encoding a fragment, preferably of a BSP, in a host cell.

Polypeptides of the present invention are also inclusive of mutants, fusion proteins, homologous proteins and allelic variants.

- 10 A mutant protein, or mutein, may have the same or different properties compared to a naturally occurring polypeptide and comprises at least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of a native polypeptide. Small deletions and insertions can often be found that do not alter the function of a protein. Muteins may or may not be breast-specific. Preferably, the
15 mutein is breast-specific. More preferably the mutein is a polypeptide that comprises at least one amino acid insertion, duplication, deletion, rearrangement or substitution compared to the amino acid sequence of SEQ ID NO: 73-179. Accordingly, in a preferred embodiment, the mutein is one that exhibits at least 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more
20 preferably at least 80% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 73-179. In a yet more preferred embodiment, the mutein exhibits at least 85%, more preferably 90%, even more preferably 95% or 96%, and yet more preferably at least 97%, 98%, 99% or 99.5% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 73-179.

- 25 A mutein may be produced by isolation from a naturally occurring mutant cell, tissue or organism. A mutein may be produced by isolation from a cell, tissue or organism that has been experimentally mutagenized. Alternatively, a mutein may be produced by chemical manipulation of a polypeptide, such as by altering the amino acid residue to another amino acid residue using synthetic or semi-synthetic chemical techniques. In a
30 preferred embodiment, a mutein is produced from a host cell comprising a mutated nucleic acid molecule compared to the naturally occurring nucleic acid molecule. For instance, one may produce a mutein of a polypeptide by introducing one or more mutations into a nucleic acid molecule of the invention and then expressing it recombinantly. These

mutations may be targeted, in which particular encoded amino acids are altered, or may be untargeted, in which random encoded amino acids within the polypeptide are altered. Muteins with random amino acid alterations can be screened for a particular biological activity or property, particularly whether the polypeptide is breast-specific, as described 5 below. Multiple random mutations can be introduced into the gene by methods well known to the art, *e.g.*, by error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, sexual PCR mutagenesis, *in vivo* mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis and site-specific mutagenesis. Methods of producing muteins with targeted or random amino acid 10 alterations are well known in the art. *See, e.g.*, Sambrook (1989), *supra*; Sambrook (2001), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), as well as U.S. Patent No. 5,223,408, which is herein incorporated by reference in its entirety.

The invention also contemplates polypeptides that are homologous to a polypeptide of the invention. In a preferred embodiment, the polypeptide is homologous 15 to a BSP. In an even more preferred embodiment, the polypeptide is homologous to a BSP selected from the group having an amino acid sequence of SEQ ID NO: 73-179. By homologous polypeptide it is meant one that exhibits significant sequence identity to a BSP, preferably a BSP having an amino acid sequence of SEQ ID NO: 73-179. By significant sequence identity it is meant that the homologous polypeptide exhibits at least 20 50% sequence identity, more preferably at least 60% sequence identity, even more preferably at least 70%, yet more preferably at least 80% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 73-179. More preferred are homologous polypeptides exhibiting at least 85%, more preferably 90%, even more 25 preferably 95% or 96%, and yet more preferably at least 97% or 98% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 73-179. Most preferably, the homologous polypeptide exhibits at least 99%, more preferably 99.5%, even more 30 preferably 99.6%, 99.7%, 99.8% or 99.9% sequence identity to a BSP comprising an amino acid sequence of SEQ ID NO: 73-179. In a preferred embodiment, the amino acid substitutions of the homologous polypeptide are conservative amino acid substitutions as discussed *supra*.

Homologous polypeptides of the present invention also comprise polypeptides encoded by a nucleic acid molecule that selectively hybridizes to a BSNA or an antisense sequence thereof. In this embodiment, it is preferred that the homologous polypeptide be

encoded by a nucleic acid molecule that hybridizes to a BSNA under low stringency, moderate stringency or high stringency conditions, as defined herein. More preferred is a homologous polypeptide encoded by a nucleic acid sequence which hybridizes to a BSNA selected from the group consisting of SEQ ID NO: 1-72 or a homologous polypeptide 5 encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule that encodes a BSP, preferably a BSP of SEQ ID NO:73-179 under low stringency, moderate stringency or high stringency conditions, as defined herein.

Homologous polypeptides of the present invention may be naturally occurring and derived from another species, especially one derived from another primate, such as 10 chimpanzee, gorilla, rhesus macaque, or baboon, wherein the homologous polypeptide comprises an amino acid sequence that exhibits significant sequence identity to that of SEQ ID NO: 73-179. The homologous polypeptide may also be a naturally occurring polypeptide from a human, when the BSP is a member of a family of polypeptides. The homologous polypeptide may also be a naturally occurring polypeptide derived from a 15 non-primate, mammalian species, including without limitation, domesticated species, *e.g.*, dog, cat, mouse, rat, rabbit, guinea pig, hamster, cow, horse, goat or pig. The homologous polypeptide may also be a naturally occurring polypeptide derived from a non-mammalian species, such as birds or reptiles. The naturally occurring homologous protein may be isolated directly from humans or other species. Alternatively, the nucleic acid molecule 20 encoding the naturally occurring homologous polypeptide may be isolated and used to express the homologous polypeptide recombinantly. The homologous polypeptide may also be one that is experimentally produced by random mutation of a nucleic acid molecule and subsequent expression of the nucleic acid molecule. Alternatively, the homologous polypeptide may be one that is experimentally produced by directed mutation 25 of one or more codons to alter the encoded amino acid of a BSP. In a preferred embodiment, the homologous polypeptide encodes a polypeptide that is a BSP.

Relatedness of proteins can also be characterized using a second functional test, such as the ability of a first protein competitively to inhibit the binding of a second protein to an antibody. It is, therefore, another aspect of the present invention to provide isolated 30 polypeptides not only identical in sequence to those described with particularity herein, but also to provide isolated polypeptides (“cross-reactive proteins”) that competitively inhibit the binding of antibodies to all or to a portion of the isolated polypeptides of the

present invention. Such competitive inhibition can readily be determined using immunoassays well known in the art.

As discussed above, single nucleotide polymorphisms (SNPs) occur frequently in eukaryotic genomes, and the sequence determined from one individual of a species may 5 differ from other allelic forms present within the population. Thus, polypeptides of the present invention are also inclusive of those encoded by an allelic variant of a nucleic acid molecule encoding a BSP. In this embodiment, it is preferred that the polypeptide be encoded by an allelic variant of a gene that encodes a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO: 73-179. More preferred is 10 that the polypeptide be encoded by an allelic variant of a gene that has the nucleic acid sequence selected from the group consisting of SEQ ID NO: 1-72.

Polypeptides of the present invention are also inclusive of derivative polypeptides encoded by a nucleic acid molecule according to the instant invention. In this embodiment, it is preferred that the polypeptide be a BSP. Also preferred are derivative 15 polypeptides having an amino acid sequence selected from the group consisting of SEQ ID NO: 73-179 and which has been acetylated, carboxylated, phosphorylated, glycosylated, ubiquitinated or post-translationally modified in another manner. In another preferred embodiment, the derivative has been labeled with, *e.g.*, radioactive isotopes such as ^{125}I , ^{32}P , ^{35}S , and ^3H . In another preferred embodiment, the derivative has been labeled 20 with fluorophores, chemiluminescent agents, enzymes, and antiligands that can serve as specific binding pair members for a labeled ligand.

Polypeptide modifications are well known to those of skill and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of 25 glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as, for instance Creighton, Protein Structure and Molecular Properties, 2nd ed., W. H. Freeman and Company (1993). Many detailed reviews are available on this subject, such as, for example, those provided by Wold, in Johnson (ed.), Posttranslational Covalent Modification of Proteins, pgs. 1-12, Academic Press (1983); 30 Seifter *et al.*, *Meth. Enzymol.* 182: 626-646 (1990) and Rattan *et al.*, *Ann. N.Y. Acad. Sci.* 663: 48-62 (1992).

One may determine whether a polypeptide of the invention is likely to be post-translationally modified by analyzing the sequence of the polypeptide to determine if there

are peptide motifs indicative of sites for post-translational modification. There are a number of computer programs that permit prediction of post-translational modifications. See, e.g., expasy.org (accessed November 11, 2002) of the world wide web, which includes PSORT, for prediction of protein sorting signals and localization sites, SignalP, 5 for prediction of signal peptide cleavage sites, MITOPROT and Predotar, for prediction of mitochondrial targeting sequences, NetOGlyc, for prediction of type O-glycosylation sites in mammalian proteins, big-PI Predictor and DGPI, for prediction of prenylation-anchor and cleavage sites, and NetPhos, for prediction of Ser, Thr and Tyr phosphorylation sites in eukaryotic proteins. Other computer programs, such as those included in GCG, also 10 may be used to determine post-translational modification peptide motifs.

General examples of types of post-translational modifications include, but are not limited to: (Z)-dehydrobutyryne; 1-chondroitin sulfate-L-aspartic acid ester; 1'-glycosyl-L-tryptophan; 1'-phospho-L-histidine; 1-thioglycine; 2'-(S-L-cysteinyl)-L-histidine; 2'-[3-carboxamido (trimethylammonio)propyl]-L-histidine; 2'-alpha-mannosyl-L-tryptophan; 2-methyl-L-glutamine; 2-oxobutanoic acid; 2-pyrrolidone carboxylic acid; 3'-(1'-L-histidyl)-L-tyrosine; 3'-(8alpha-FAD)-L-histidine; 3'-(S-L-cysteinyl)-L-tyrosine; 3', 3", 5'-triiodo-L-thyronine; 3'-4'-phospho-L-tyrosine; 3-hydroxy-L-proline; 3'-methyl-L-histidine; 3-methyl-L-lanthionine; 3'-phospho-L-histidine; 4'-(L-tryptophan)-L-tryptophyl quinone; 42 N-cysteinyl-glycosylphosphatidylinositolethanolamine; 43 -(T-L-histidyl)-L-tyrosine; 4-hydroxy-L-arginine; 4-hydroxy-L-lysine; 4-hydroxy-L-proline; 5'-(N6-L-lysine)-L-topoquinone; 5-hydroxy-L-lysine; 5-methyl-L-arginine; alpha-L-microglobulin-Ig alpha complex chromophore; bis-L-cysteinyl bis-L-histidino diiron disulfide; bis-L--cysteinyl-L-N3'-histidino-L-serinyI tetrailron' tetrasulfide; chondroitin sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; D-alanine; D-allo-isoleucine; D-asparagine; 25 dehydroalanine; dehydrotyrosine; dermatan 4-sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; D-glucuronyl-N-glycine; dipyrrolylmethanemethyl-L-cysteine; D-leucine; D-methionine; D-phenylalanine; D-serine; D-tryptophan; glycine amide; glycine oxazolecarboxylic acid; glycine thiazolecarboxylic acid; heme P450-bis-L-cysteine-L-tyrosine; heme-bis-L-cysteine; hemediol-L-aspartyL ester-L-glutamyl ester; 30 hemediol-L-aspartyL ester-L-glutamyl ester-L-methionine sulfonium; heme-L-cysteine; heme-L-histidine; heparan sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-serine; heme P450-bis-L-cysteine-L-lysine; hexakis-L-cysteinyl hexairon hexasulfide; keratan sulfate D-glucuronyl-D-galactosyl-D-galactosyl-D-xylosyl-L-threonine; L

oxoalanine- lactic acid; L phenyllactic acid; l'-(8alpha-FAD)-L-histidine; L-2',4',5'-topaquinone; L-3',4'-dihydroxyphenylalanine; L-3',4',5'-trihydroxyphenylalanine; L-4'-bromophenylalanine; L-6'-bromotryptophan; L-alanine amide; L-alanyl imidazolinone glycine; L-allysine; L-arginine amide; L-asparagine amide; L-aspartic 4-phosphoric anhydride; L-aspartic acid 1-amide; L-beta-methylthioaspartic acid; L-bromohistidine; L-citrulline; L-cysteine amide; L-cysteine glutathione disulfide; L-cysteine methyl disulfide; L-cysteine methyl ester; L-cysteine oxazolecarboxylic acid; L-cysteine oxazolinecarboxylic acid; L-cysteine persulfide; L-cysteine sulfenic acid; L-cysteine sulfenic acid; L-cysteine thiazolecarboxylic acid; L-cysteinyl homocitryl molybdenum-5-heptaiiron-nonasulfide; L-cysteinyl imidazolinone glycine; L-cysteinyl molybdopterin; L-cysteinyl molybdopterin guanine dinucleotide; L-cystine; L-erythro-beta-hydroxyasparagine; L-erythro-beta-hydroxyaspartic acid; L-gamma-carboxyglutamic acid; L-glutamic acid 1-amide; L-glutamic acid 5-methyl ester; L-glutamine amide; L-glutamyl 5-glycerylphosphorylethanolarnine; L-histidine amide; L-isoglutamyl-polyglutamic acid; L-isoglutamyl-polyglycine; L-isoleucine amide; L-lanthionine; L-leucine amide; L-lysine amide; L-lysine thiazolecarboxylic acid; L-lysinoalanine; L-methionine amide; L-methionine sulfone; L-phenyalanine thiazolecarboxylic acid; L-phenylalanine amide; L-proline amide; L-selenocysteine; L-selenocysteinyl molybdopterin guanine dinucleotide; L-serine amide; L-serine thiazolecarboxylic acid; L-seryl imidazolinone glycine; L-T-bromophenylalanine; L-T-bromophenylalanine; L-threonine amide; L-thyroxine; L-tryptophan amide; L-tryptophyl quinone; L-tyrosine amide; L-valine amide; meso-lanthionine; N-(L-glutamyl)-L-tyrosine; N-(L-isoaspartyl)-glycine; N-(L-isoaspartyl)-L-cysteine; N,N,N-trimethyl-L-alanine; N,N-dimethyl-L-proline; N2-acetyl-L-lysine; N2-succinyl-L-tryptophan; N4-(ADP-ribosyl)-L-asparagine; N4-glycosyl-L-asparagine; N4-hydroxymethyl-L-asparagine; N4-methyl-L-asparagine; N5-methyl-L-glutamine; N6-1-carboxyethyl-L-lysine; N6-(4-amino hydroxybutyl)-L-lysine; N6-(L-isoglutamyl)-L-lysine; N6-(phospho-5'-adenosine)-L-lysine; N6-(phospho-5'-guanosine)-L-lysine; N6,N6,N6-trimethyl-L-lysine; N6,N6-dimethyl-L-lysine; N6-acetyl-L-lysine; N6-biotinyl-L-lysine; N6-carboxy-L-lysine; N6-formyl-L-lysine; N6-glycyl-L-lysine; N6-lipoyl-L-lysine; N6-methyl-L-lysine; N6-methyl-N6-poly(N-methyl-propylamine)-L-lysine; N6-mureinyl-L-lysine; N6-myristoyl-L-lysine; N6-palmitoyl-L-lysine; N6-pyridoxal phosphate-L-lysine; N6-pyruvic acid 2-iminyl-L-lysine; N6-retinal-L-lysine; N-acetylglycine; N-acetyl-L-glutamine; N-acetyl-L-alanine; N-acetyl-L-aspartic acid; N-

acetyl-L-cysteine; N-acetyl-L-glutamic acid; N-acetyl-L-isoleucine; N-acetyl-L-methionine; N-acetyl-L-proline; N-acetyl-L-serine; N-acetyl-L-threonine; N-acetyl-L-tyrosine; N-acetyl-L-valine; N-alanyl-glycosylphosphatidylinositolethanolamine; N-asparaginyl-glycosylphosphatidylinositolethanolarnine; N-aspartyl-

5 glycosylphosphatidylinositolethanolamine; N-formylglycine; N-formyl-L-methionine; N-glycyl-glycosylphosphatidylinositolethanolamine; N-L-glutamyl-poly-L-glutamic acid; N-methylglycine; N-methyl-L-alanine; N-methyl-L-methionine; N-methyl-L-phenylalanine; N-myristoyl-glycine; N-palmitoyl-L-cysteine; N-pyruvic acid 2-iminyl-L-cysteine; N-pyruvic acid 2-iminyl-L-valine; N-seryl-glycosylphosphatidylinositolethanolamine; N-

10 seryl-glycosyBSPingolipidinositolethanolamine; O-(ADP-ribosyl)-L-serine; O-(phospho-5'-adenosine)-L-threonine; O-(phospho-5'-DNA)-L-serine; O-(phospho-5'-DNA)-L-threonine; O-(phospho-5'rRNA)-L-serine; O-(phosphoribosyl dephospho-coenzyme A)-L-serine; O-(sn-1-glycerophosphoryl)-L-serine; O4'-(8alpha-FAD)-L-tyrosine; O4'-(phospho-5'-adenosine)-L-tyrosine; O4'-(phospho-5'-DNA)-L-tyrosine; O4'-(phospho-5'-RNA)-L-

15 tyrosine; O4'-(phospho-5'-uridine)-L-tyrosine; O4-glycosyl-L-hydroxyproline; O4'-glycosyl-L-tyrosine; O4'-sulfo-L-tyrosine; O5-glycosyl-L-hydroxylysine; O-glycosyl-L-serine; O-glycosyl-L-threonine; omega-N-(ADP-ribosyl)-L-arginine; omega-N-omega-N'-dimethyl-L-arginine; omega-N-methyl-L-arginine; omega-N-omega-N-dimethyl-L-arginine; omega-N-phospho-L-arginine; O'octanoyl-L-serine; O-palmitoyl-L-serine; O-

20 palmitoyl-L-threonine; O-phospho-L-serine; O-phospho-L-threonine; O-phosphopantetheine-L-serine; phycoerythrobilin-bis-L-cysteine; phycourobilin-bis-L-cysteine; pyrroloquinoline quinone; pyruvic acid; S hydroxycinnamyl-L-cysteine; S-(2-aminovinyl) methyl-D-eysteine; S-(2-aminovinyl)-D-cysteine; S-(6-FW-L-cysteine; S-(8alpha-FAD)-L-cysteine; S-(ADP-ribosyl)-L-cysteine; S-(L-isoglutamyl)-L-cysteine; S-

25 12-hydroxyfarnesyl-L-cysteine; S-acetyl-L-cysteine; S-diacylglycerol-L-cysteine; S-diphytanoylglycerot diether-L-cysteine; S-farnesyl-L-cysteine; S-geranylgeranyl-L-cysteine; S-glycosyl-L-cysteine; S-glycyl-L-cysteine; S-methyl-L-cysteine; S-nitrosyl-L-cysteine; S-palmitoyl-L-cysteine; S-phospho-L-cysteine; S-phycobiliviolin-L-cysteine; S-phycocyanobilin-L-cysteine; S-phycoerythrobilin-L-cysteine; S-phytochromobilin-L-

30 cysteine; S-selenyl-L-cysteine; S-sulfo-L-cysteine; tetrakis-L-cysteinyl diiron disulfide; tetrakis-L-cysteinyl iron; tetrakis-L-cysteinyl tetrairon tetrasulfide; trans-2,3-cis 4-dihydroxy-L-proline; tris-L-cysteinyl triiron tetrasulfide; tris-L-cysteinyl triiron trisulfide; tris-L-cysteinyl-L-aspartato tetrairon tetrasulfide; tris-L-cysteinyl-L-cysteine persulfido-

bis-L-glutamato-L-histidino tetrairon disulfide trioxide; tris-L-cysteinyl-L-N3'-histidino tetrairon tetrasulfide; tris-L-cysteinyl-L-N1'-histidino tetrairon tetrasulfide; and tris-L-cysteinyl-L-serinyl tetrairon tetrasulfide.

Additional examples of PTMs may be found in web sites such as the Delta Mass database based on Krishna, R. G. and F. Wold (1998). Posttranslational Modifications. Proteins - Analysis and Design. R. H. Angeletti. San Diego, Academic Press. 1: 121-206; Methods in Enzymology, 193, J.A. McClosky (ed) (1990), pages 647-660; Methods in Protein Sequence Analysis edited by Kazutomo Imahori and Fumio Sakiyama, Plenum Press, (1993) "Post-translational modifications of proteins" R.G. Krishna and F. Wold pages 167-172; "GlycoSuiteDB: a new curated relational database of glycoprotein glycan structures and their biological sources" Cooper et al. Nucleic Acids Res. 29; 332-335 (2001) "O-GLYCBASE version 4.0: a revised database of O-glycosylated proteins" Gupta et al. Nucleic Acids Research, 27: 370-372 (1999); and "PhosphoBase, a database of phosphorylation sites: release 2.0.", Kreegipuu et al. Nucleic Acids Res 27(1):237-239 (1999) see also, WO 02/21139A2, the disclosure of which is incorporated herein by reference in its entirety.

Tumorigenesis is often accompanied by alterations in the post-translational modifications of proteins. Thus, in another embodiment, the invention provides polypeptides from cancerous cells or tissues that have altered post-translational modifications compared to the post-translational modifications of polypeptides from normal cells or tissues. A number of altered post-translational modifications are known. One common alteration is a change in phosphorylation state, wherein the polypeptide from the cancerous cell or tissue is hyperphosphorylated or hypophosphorylated compared to the polypeptide from a normal tissue, or wherein the polypeptide is phosphorylated on different residues than the polypeptide from a normal cell. Another common alteration is a change in glycosylation state, wherein the polypeptide from the cancerous cell or tissue has more or less glycosylation than the polypeptide from a normal tissue, and/or wherein the polypeptide from the cancerous cell or tissue has a different type of glycosylation than the polypeptide from a noncancerous cell or tissue. Changes in glycosylation may be critical because carbohydrate-protein and carbohydrate-carbohydrate interactions are important in cancer cell progression, dissemination and invasion. See, e.g., Barchi, *Curr. Pharm. Des.* 6: 485-501 (2000), Verma, *Cancer Biochem. Biophys.* 14: 151-162 (1994) and Dennis et al., *Bioessays* 5: 412-421 (1999).

Another post-translational modification that may be altered in cancer cells is prenylation. Prenylation is the covalent attachment of a hydrophobic prenyl group (either farnesyl or geranylgeranyl) to a polypeptide. Prenylation is required for localizing a protein to a cell membrane and is often required for polypeptide function. For instance, 5 the Ras superfamily of GTPase signalling proteins must be prenylated for function in a cell. See, e.g., Prendergast et al., *Semin. Cancer Biol.* 10: 443-452 (2000) and Khwaja et al., *Lancet* 355: 741-744 (2000).

Other post-translation modifications that may be altered in cancer cells include, without limitation, polypeptide methylation, acetylation, arginylation or racemization of 10 amino acid residues. In these cases, the polypeptide from the cancerous cell may exhibit either increased or decreased amounts of the post-translational modification compared to the corresponding polypeptides from noncancerous cells.

Other polypeptide alterations in cancer cells include abnormal polypeptide cleavage of proteins and aberrant protein-protein interactions. Abnormal polypeptide 15 cleavage may be cleavage of a polypeptide in a cancerous cell that does not usually occur in a normal cell, or a lack of cleavage in a cancerous cell, wherein the polypeptide is cleaved in a normal cell. Aberrant protein-protein interactions may be either covalent cross-linking or non-covalent binding between proteins that do not normally bind to each other. Alternatively, in a cancerous cell, a protein may fail to bind to another protein to 20 which it is bound in a noncancerous cell. Alterations in cleavage or in protein-protein interactions may be due to over- or underproduction of a polypeptide in a cancerous cell compared to that in a normal cell, or may be due to alterations in post-translational modifications (see above) of one or more proteins in the cancerous cell. See, e.g., Henschen-Edman, *Ann. N.Y. Acad. Sci.* 936: 580-593 (2001).

25 Alterations in polypeptide post-translational modifications, as well as changes in polypeptide cleavage and protein-protein interactions, may be determined by any method known in the art. For instance, alterations in phosphorylation may be determined by using anti-phosphoserine, anti-phosphothreonine or anti-phosphotyrosine antibodies or by amino acid analysis. Glycosylation alterations may be determined using antibodies specific for 30 different sugar residues, by carbohydrate sequencing, or by alterations in the size of the glycoprotein, which can be determined by, e.g., SDS polyacrylamide gel electrophoresis (PAGE). Other alterations of post-translational modifications, such as prenylation, racemization, methylation, acetylation and arginylation, may be determined by chemical

analysis, protein sequencing, amino acid analysis, or by using antibodies specific for the particular post-translational modifications. Changes in protein-protein interactions and in polypeptide cleavage may be analyzed by any method known in the art including, without limitation, non-denaturing PAGE (for non-covalent protein-protein interactions), SDS

- 5 PAGE (for covalent protein-protein interactions and protein cleavage), chemical cleavage, protein sequencing or immunoassays.

In another embodiment, the invention provides polypeptides that have been post-translationally modified. In one embodiment, polypeptides may be modified enzymatically or chemically, by addition or removal of a post-translational modification.

- 10 For example, a polypeptide may be glycosylated or deglycosylated enzymatically. Similarly, polypeptides may be phosphorylated using a purified kinase, such as a MAP kinase (e.g., p38, ERK, or JNK) or a tyrosine kinase (e.g., Src or erbB2). A polypeptide may also be modified through synthetic chemistry. Alternatively, one may isolate the polypeptide of interest from a cell or tissue that expresses the polypeptide with the desired 15 post-translational modification. In another embodiment, a nucleic acid molecule encoding the polypeptide of interest is introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide in the desired fashion. If the polypeptide does not contain a motif for a desired post-translational modification, one may alter the post-translational modification by mutating the nucleic acid sequence of a nucleic 20 acid molecule encoding the polypeptide so that it contains a site for the desired post-translational modification. Amino acid sequences that may be post-translationally modified are known in the art. See, e.g., the programs described above on the website expasy.org of the world wide web. The nucleic acid molecule may also be introduced into a host cell that is capable of post-translationally modifying the encoded polypeptide.
- 25 Similarly, one may delete sites that are post-translationally modified by either mutating the nucleic acid sequence so that the encoded polypeptide does not contain the post-translational modification motif, or by introducing the native nucleic acid molecule into a host cell that is not capable of post-translationally modifying the encoded polypeptide.

- It will be appreciated, as is well known and as noted above, that polypeptides are 30 not always entirely linear. For instance, polypeptides may be branched as a result of ubiquitination, and they may be circular, with or without branching, generally as a result of posttranslational events, including natural processing events and events brought about by human manipulation which do not occur naturally. Circular, branched and branched

circular polypeptides may be synthesized by non-translation natural processes and by entirely synthetic methods, as well. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. In fact, blockage of the amino or carboxyl group in a polypeptide, or both, by a 5 covalent modification, is common in naturally occurring and synthetic polypeptides and such modifications may be present in polypeptides of the present invention, as well. For instance, the amino terminal residue of polypeptides made in *E. coli*, prior to proteolytic processing, almost invariably will be N-formylmethionine.

Useful post-synthetic (and post-translational) modifications include conjugation to 10 detectable labels, such as fluorophores. A wide variety of amine-reactive and thiol-reactive fluorophore derivatives have been synthesized that react under nondenaturing conditions with N-terminal amino groups and epsilon amino groups of lysine residues, on the one hand, and with free thiol groups of cysteine residues, on the other.

Kits are available commercially that permit conjugation of proteins to a variety of 15 amine-reactive or thiol-reactive fluorophores: Molecular Probes, Inc. (Eugene, OR, USA), *e.g.*, offers kits for conjugating proteins to Alexa Fluor 350, Alexa Fluor 430, Fluorescein-EX, Alexa Fluor 488, Oregon Green 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, and Texas Red-X.

A wide variety of other amine-reactive and thiol-reactive fluorophores are 20 available commercially (Molecular Probes, Inc., Eugene, OR, USA), including Alexa Fluor® 350, Alexa Fluor® 488, Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, 25 BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from Molecular Probes, Inc., Eugene, OR, USA).

The polypeptides of the present invention can also be conjugated to fluorophores, 30 other proteins, and other macromolecules, using bifunctional linking reagents. Common homobifunctional reagents include, *e.g.*, APG, AEDP, BASED, BMB, BMDB, BMH, BMOE, BM[PEO]3, BM[PEO]4, BS3, BSOCOES, DFDNB, DMA, DMP, DMS, DPPPB,

DSG, DSP (Lomant's Reagent), DSS, DST, DTBP, DTME, DTSSP, EGS, HBVS, Sulfo-BSOCOES, Sulfo-DST, Sulfo-EGS (all available from Pierce, Rockford, IL, USA); common heterobifunctional cross-linkers include ABH, AMAS, ANB-NOS, APDP, ASBA, BMPA, BMPH, BMPS, EDC, EMCA, EMCH, EMCS, KMUA, KMUH, GMBS, 5 LC-SMCC, LC-SPDP, MBS, M2C2H, MPBH, MSA, NHS-ASA, PDPH, PMPI, SADP, SAED, SAND, SANPAH, SASD, SATP, SBAP, SFAD, SIA, SIAB, SMCC, SMPB, SMPH, SMPT, SPDP, Sulfo-EMCS, Sulfo-GMBS, Sulfo-HSAB, Sulfo-KMUS, Sulfo-LC-SPDP, Sulfo-MBS, Sulfo-NHS-LC-ASA, Sulfo-SADP, Sulfo-SANPAH, Sulfo-SIAB, Sulfo-SMCC, Sulfo-SMPB, Sulfo-LC-SMPT, SVSB, TFCS (all available 10 Pierce, Rockford, IL, USA).

Polypeptides of the present invention, including full length polypeptides, fragments and fusion proteins, can be conjugated, using such cross-linking reagents, to fluorophores that are not amine- or thiol-reactive. Other labels that usefully can be conjugated to polypeptides of the present invention include radioactive labels, 15 echosonographic contrast reagents, and MRI contrast agents.

Polypeptides of the present invention, including full length polypeptides, fragments and fusion proteins, can also usefully be conjugated using cross-linking agents to carrier proteins, such as KLH, bovine thyroglobulin, and even bovine serum albumin (BSA), to increase immunogenicity for raising anti-BSP antibodies.

20 Polypeptides of the present invention, including full length polypeptides, fragments and fusion proteins, can also usefully be conjugated to polyethylene glycol (PEG); PEGylation increases the serum half life of proteins administered intravenously for replacement therapy. Delgado *et al.*, *Crit. Rev. Ther. Drug Carrier Syst.* 9(3-4): 249-304 (1992); Scott *et al.*, *Curr. Pharm. Des.* 4(6): 423-38 (1998); De Santis *et al.*, *Curr. Opin. Biotechnol.* 10(4): 324-30 (1999). PEG monomers can be attached to the protein directly 25 or through a linker, with PEGylation using PEG monomers activated with tresyl chloride (2,2,2-trifluoroethanesulphonyl chloride) permitting direct attachment under mild conditions.

30 Polypeptides of the present invention are also inclusive of analogs of a polypeptide encoded by a nucleic acid molecule according to the instant invention. In a preferred embodiment, this polypeptide is a BSP. In a more preferred embodiment, this polypeptide is derived from a polypeptide having part or all of the amino acid sequence of SEQ ID NO: 73-179. Also preferred is an analog polypeptide comprising one or more

substitutions of non-natural amino acids or non-native inter-residue bonds compared to the naturally occurring polypeptide. In one embodiment, the analog is structurally similar to a BSP, but one or more peptide linkages is replaced by a linkage selected from the group consisting of --CH₂NH--, --CH₂S--, --CH₂-CH₂--, --CH=CH--(cis and trans), --COCH₂--,

5 --CH(OH)CH₂-- and --CH₂SO--. In another embodiment, the analog comprises substitution of one or more amino acids of a BSP with a D-amino acid of the same type or other non-natural amino acid in order to generate more stable peptides. D-amino acids can readily be incorporated during chemical peptide synthesis: peptides assembled from D-amino acids are more resistant to proteolytic attack; incorporation of D-amino acids can

10 also be used to confer specific three-dimensional conformations on the peptide. Other amino acid analogues commonly added during chemical synthesis include ornithine, norleucine, phosphorylated amino acids (typically phosphoserine, phosphothreonine, phosphotyrosine), L-malonyltyrosine, a non-hydrolyzable analog of phosphotyrosine (*see, e.g.*, Kole *et al.*, *Biochem. Biophys. Res. Com.* 209: 817-821 (1995)), and various

15 halogenated phenylalanine derivatives.

Non-natural amino acids can be incorporated during solid phase chemical synthesis or by recombinant techniques, although the former is typically more common. Solid phase chemical synthesis of peptides is well established in the art. Procedures are described, *inter alia*, in Chan *et al.* (eds.), Fmoc Solid Phase Peptide Synthesis: A Practical Approach (Practical Approach Series), Oxford Univ. Press (March 2000); Jones, Amino Acid and Peptide Synthesis (Oxford Chemistry Primers, No 7), Oxford Univ. Press (1992); and Bodanszky, Principles of Peptide Synthesis (Springer Laboratory), Springer Verlag (1993).

Amino acid analogues having detectable labels are also usefully incorporated

25 during synthesis to provide derivatives and analogs. Biotin, for example can be added using biotinoyl-(9-fluorenylmethoxycarbonyl)-L-lysine (FMOC biocytin) (Molecular Probes, Eugene, OR, USA). Biotin can also be added enzymatically by incorporation into a fusion protein of an *E. coli* BirA substrate peptide. The FMOC and *t*BOC derivatives of dabcyl-L-lysine (Molecular Probes, Inc., Eugene, OR, USA) can be used to incorporate

30 the dabcyl chromophore at selected sites in the peptide sequence during synthesis. The aminonaphthalene derivative EDANS, the most common fluorophore for pairing with the dabcyl quencher in fluorescence resonance energy transfer (FRET) systems, can be

introduced during automated synthesis of peptides by using EDANS-FMOC-L-glutamic acid or the corresponding *t*BOC derivative (both from Molecular Probes, Inc., Eugene, OR, USA). Tetramethylrhodamine fluorophores can be incorporated during automated FMOC synthesis of peptides using (FMOC)-TMR-L-lysine (Molecular Probes, Inc. 5 Eugene, OR, USA).

Other useful amino acid analogues that can be incorporated during chemical synthesis include aspartic acid, glutamic acid, lysine, and tyrosine analogues having allyl side-chain protection (Applied Biosystems, Inc., Foster City, CA, USA); the allyl side chain permits synthesis of cyclic, branched-chain, sulfonated, glycosylated, and 10 phosphorylated peptides.

A large number of other FMOC-protected non-natural amino acid analogues capable of incorporation during chemical synthesis are available commercially, including, e.g., Fmoc-2-aminobicyclo[2.2.1]heptane-2-carboxylic acid, Fmoc-3-endo-aminobicyclo[2.2.1]heptane-2-endo-carboxylic acid, Fmoc-3-exo-aminobicyclo[2.2.1]heptane-2-exo-carboxylic acid, Fmoc-3-endo-amino-bicyclo[2.2.1]hept-5-ene-2-exo-carboxylic acid, Fmoc-cis-2-amino-1-cyclohexanecarboxylic acid, Fmoc-trans-2-amino-1-cyclohexanecarboxylic acid, Fmoc-1-amino-1-cyclopentanecarboxylic acid, Fmoc-cis-2-amino-1-cyclopentanecarboxylic acid, Fmoc-1-amino-1-cyclopropanecarboxylic acid, Fmoc-D-2-amino-4-(ethylthio)butyric acid, Fmoc-L-2-amino-4-(ethylthio)butyric acid, Fmoc-L-buthionine, Fmoc-S-methyl-L-Cysteine, Fmoc-2-aminobenzoic acid (anthranillic acid), Fmoc-3-aminobenzoic acid, Fmoc-4-aminobenzoic acid, Fmoc-2-aminobenzophenone-2'-carboxylic acid, Fmoc-N-(4-aminobenzoyl)- β -alanine, Fmoc-2-amino-4,5-dimethoxybenzoic acid, Fmoc-4-aminohippuric acid, Fmoc-2-amino-3-hydroxybenzoic acid, Fmoc-2-amino-5-hydroxybenzoic acid, Fmoc-3-amino-4-hydroxybenzoic acid, Fmoc-4-amino-3-hydroxybenzoic acid, Fmoc-4-amino-2-hydroxybenzoic acid, Fmoc-5-amino-2-hydroxybenzoic acid, Fmoc-2-amino-3-methoxybenzoic acid, Fmoc-4-amino-3-methoxybenzoic acid, Fmoc-2-amino-3-methylbenzoic acid, Fmoc-2-amino-5-methylbenzoic acid, Fmoc-2-amino-6-methylbenzoic acid, Fmoc-3-amino-2-methylbenzoic acid, Fmoc-3-amino-4-methylbenzoic acid, Fmoc-4-amino-3-methylbenzoic acid, Fmoc-3-amino-2-naphtoic acid, Fmoc-D,L-3-amino-3-phenylpropionic acid, Fmoc-L-Methyldopa, Fmoc-2-amino-4,6-dimethyl-3-

pyridinecarboxylic acid, Fmoc-D,L-amino-2-thiophenacetic acid, Fmoc-4-(carboxymethyl)piperazine, Fmoc-4-carboxypiperazine, Fmoc-4-(carboxymethyl)homopiperazine, Fmoc-4-phenyl-4-piperidinecarboxylic acid, Fmoc-L-1,2,3,4-tetrahydronorharman-3-carboxylic acid, Fmoc-L-thiazolidine-4-carboxylic acid, all 5 available from The Peptide Laboratory (Richmond, CA, USA).

Non-natural residues can also be added biosynthetically by engineering a suppressor tRNA, typically one that recognizes the UAG stop codon, by chemical aminoacylation with the desired unnatural amino acid. Conventional site-directed mutagenesis is used to introduce the chosen stop codon UAG at the site of interest in the 10 protein gene. When the acylated suppressor tRNA and the mutant gene are combined in an *in vitro* transcription/translation system, the unnatural amino acid is incorporated in response to the UAG codon to give a protein containing that amino acid at the specified position. Liu *et al.*, *Proc. Natl Acad. Sci. USA* 96(9): 4780-5 (1999); Wang *et al.*, *Science* 292(5516): 498-500 (2001).

15 *Fusion Proteins*

Another aspect of the present invention relates to the fusion of a polypeptide of the present invention to heterologous polypeptides. In a preferred embodiment, the polypeptide of the present invention is a BSP. In a more preferred embodiment, the polypeptide of the present invention that is fused to a heterologous polypeptide which 20 comprises part or all of the amino acid sequence of SEQ ID NO: 73-179, or is a mutein, homologous polypeptide, analog or derivative thereof. In an even more preferred embodiment, the fusion protein is encoded by a nucleic acid molecule comprising all or part of the nucleic acid sequence of SEQ ID NO: 1-72, or comprises all or part of a nucleic acid sequence that selectively hybridizes or is homologous to a nucleic acid molecule 25 comprising a nucleic acid sequence of SEQ ID NO: 1-72.

The fusion proteins of the present invention will include at least one fragment of a polypeptide of the present invention, which fragment is at least 6, typically at least 8, often at least 15, and usefully at least 16, 17, 18, 19, or 20 amino acids long. The fragment of the polypeptide of the present to be included in the fusion can usefully be at least 25 30 amino acids long, at least 50 amino acids long, and can be at least 75, 100, or even 150 amino acids long. Fusions that include the entirety of a polypeptide of the present invention have particular utility.

The heterologous polypeptide included within the fusion protein of the present invention is at least 6 amino acids in length, often at least 8 amino acids in length, and preferably at least 15, 20, or 25 amino acids in length. Fusions that include larger polypeptides, such as the IgG Fc region, and even entire proteins (such as GFP 5 chromophore-containing proteins) are particularly useful.

As described above in the description of vectors and expression vectors of the present invention, which discussion is incorporated here by reference in its entirety, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those designed to facilitate purification and/or visualization of 10 recombinantly-expressed proteins. *See, e.g., Ausubel, Chapter 16, (1992), supra.* Although purification tags can also be incorporated into fusions that are chemically synthesized, chemical synthesis typically provides sufficient purity that further purification by HPLC suffices; however, visualization tags as above described retain their utility even when the protein is produced by chemical synthesis, and when so included 15 render the fusion proteins of the present invention useful as directly detectable markers of the presence of a polypeptide of the invention.

As also discussed above, heterologous polypeptides to be included in the fusion proteins of the present invention can usefully include those that facilitate secretion of recombinantly expressed proteins into the periplasmic space or extracellular milieu for 20 prokaryotic hosts or into the culture medium for eukaryotic cells through incorporation of secretion signals and/or leader sequences. For example, a His⁶ tagged protein can be purified on a Ni affinity column and a GST fusion protein can be purified on a glutathione affinity column. Similarly, a fusion protein comprising the Fc domain of IgG can be purified on a Protein A or Protein G column and a fusion protein comprising an epitope 25 tag such as myc can be purified using an immunoaffinity column containing an anti-c-myc antibody. It is preferable that the epitope tag be separated from the protein encoded by the essential gene by an enzymatic cleavage site that can be cleaved after purification. See also the discussion of nucleic acid molecules encoding fusion proteins that may be expressed on the surface of a cell.

30 Other useful fusion proteins of the present invention include those that permit use of the polypeptide of the present invention as bait in a yeast two-hybrid system. *See Bartel et al. (eds.), The Yeast Two-Hybrid System, Oxford University Press (1997); Zhu et al., Yeast Hybrid Technologies, Eaton Publishing (2000); Fields et al., Trends Genet.*

10(8): 286-92 (1994); Mendelsohn *et al.*, *Curr. Opin. Biotechnol.* 5(5): 482-6 (1994); Luban *et al.*, *Curr. Opin. Biotechnol.* 6(1): 59-64 (1995); Allen *et al.*, *Trends Biochem. Sci.* 20(12): 511-6 (1995); Drees, *Curr. Opin. Chem. Biol.* 3(1): 64-70 (1999); Topcu *et al.*, *Pharm. Res.* 17(9): 1049-55 (2000); Fashena *et al.*, *Gene* 250(1-2): 1-14 (2000); Colas 5 *et al.*, *Nature* 380, 548-550 (1996); Norman, T. *et al.*, *Science* 285, 591-595 (1999); Fabbrizio *et al.*, *Oncogene* 18, 4357-4363 (1999); Xu *et al.*, *Proc Natl Acad Sci U S A.* 94, 12473-12478 (1997); Yang, *et al.*, *Nuc. Acids Res.* 23, 1152-1156 (1995); Kolonin *et al.*, *Proc Natl Acad Sci U S A* 95, 14266-14271 (1998); Cohen *et al.*, *Proc Natl Acad Sci U S A* 95, 14272-14277 (1998); Uetz, *et al.* *Nature* 403, 623-627(2000); Ito, *et al.*, *Proc Natl Acad Sci U S A* 98, 4569-4574 (2001). Typically, such fusion is to either *E. coli* LexA or yeast GAL4 DNA binding domains. Related bait plasmids are available that express the bait fused to a nuclear localization signal.

Other useful fusion proteins include those that permit display of the encoded polypeptide on the surface of a phage or cell, fusions to intrinsically fluorescent proteins, 15 such as green fluorescent protein (GFP), and fusions to the IgG Fc region, as described above.

The polypeptides of the present invention can also usefully be fused to protein toxins, such as Pseudomonas exotoxin A, diphtheria toxin, shiga toxin A, anthrax toxin lethal factor, or ricin, in order to effect ablation of cells that bind or take up the proteins of 20 the present invention.

Fusion partners include, *inter alia*, myc, hemagglutinin (HA), GST, immunoglobulins, β-galactosidase, biotin trpE, protein A, β-lactamase, α-amylase, maltose binding protein, alcohol dehydrogenase, polyhistidine (for example, six histidine at the amino and/or carboxyl terminus of the polypeptide), lacZ, green fluorescent protein 25 (GFP), yeast α mating factor, GAL4 transcription activation or DNA binding domain, luciferase, and serum proteins such as ovalbumin, albumin and the constant domain of IgG. See, e.g., Ausubel (1992), *supra* and Ausubel (1999), *supra*. Fusion proteins may also contain sites for specific enzymatic cleavage, such as a site that is recognized by enzymes such as Factor XIII, trypsin, pepsin, or any other enzyme known in the art. 30 Fusion proteins will typically be made by either recombinant nucleic acid methods, as described above, chemically synthesized using techniques well known in the art (e.g., a Merrifield synthesis), or produced by chemical cross-linking.

Another advantage of fusion proteins is that the epitope tag can be used to bind the fusion protein to a plate or column through an affinity linkage for screening binding proteins or other molecules that bind to the BSP.

As further described below, the polypeptides of the present invention can readily
5 be used as specific immunogens to raise antibodies that specifically recognize
polypeptides of the present invention including BSPs and their allelic variants and
homologues. The antibodies, in turn, can be used, *inter alia*, specifically to assay for the
polypeptides of the present invention, particularly BSPs, *e.g.* by ELISA for detection of
protein fluid samples, such as serum, by immunohistochemistry or laser scanning
10 cytometry, for detection of protein in tissue samples, or by flow cytometry, for detection
of intracellular protein in cell suspensions, for specific antibody-mediated isolation and/or
purification of BSPs, as for example by immunoprecipitation, and for use as specific
agonists or antagonists of BSPs.

One may determine whether polypeptides of the present invention including BSPs,
15 muteins, homologous proteins or allelic variants or fusion proteins of the present invention
are functional by methods known in the art. For instance, residues that are tolerant of
change while retaining function can be identified by altering the polypeptide at known
residues using methods known in the art, such as alanine scanning mutagenesis,
Cunningham *et al.*, *Science* 244(4908): 1081-5 (1989); transposon linker scanning
20 mutagenesis, Chen *et al.*, *Gene* 263(1-2): 39-48 (2001); combinations of homolog- and
alanine-scanning mutagenesis, Jin *et al.*, *J. Mol. Biol.* 226(3): 851-65 (1992); and
combinatorial alanine scanning, Weiss *et al.*, *Proc. Natl. Acad. Sci USA* 97(16): 8950-4
(2000), followed by functional assay. Transposon linker scanning kits are available
commercially (New England Biolabs, Beverly, MA, USA, catalog. no. E7-102S;
25 EZ::TN™ In-Frame Linker Insertion Kit, catalogue no. EZI04KN, (Epicentre
Technologies Corporation, Madison, WI, USA).

Purification of the polypeptides or fusion proteins of the present invention is well
known and within the skill of one having ordinary skill in the art. *See, e.g.*, Scopes,
Protein Purification, 2d ed. (1987). Purification of recombinantly expressed polypeptides
30 is described above. Purification of chemically-synthesized peptides can readily be
effected, *e.g.*, by HPLC.

Accordingly, it is an aspect of the present invention to provide the isolated
polypeptides or fusion proteins of the present invention in pure or substantially pure form

in the presence or absence of a stabilizing agent. Stabilizing agents include both proteinaceous and non-proteinaceous material and are well known in the art. Stabilizing agents, such as albumin and polyethylene glycol (PEG) are known and are commercially available.

5 Although high levels of purity are preferred when the isolated polypeptide or fusion protein of the present invention are used as therapeutic agents, such as in vaccines and replacement therapy, the isolated polypeptides of the present invention are also useful at lower purity. For example, partially purified polypeptides of the present invention can be used as immunogens to raise antibodies in laboratory animals.

10 In a preferred embodiment, the purified and substantially purified polypeptides of the present invention are in compositions that lack detectable ampholytes, acrylamide monomers, bis-acrylamide monomers, and polyacrylamide.

15 The polypeptides or fusion proteins of the present invention can usefully be attached to a substrate. The substrate can be porous or solid, planar or non-planar; the bond can be covalent or noncovalent. For example, the peptides of the invention may be stabilized by covalent linkage to albumin. See, U.S. Patent No. 5,876,969, the contents of which are hereby incorporated in its entirety.

20 The polypeptides or fusion proteins of the present invention can also be usefully bound to a porous substrate, commonly a membrane, typically comprising nitrocellulose, polyvinylidene fluoride (PVDF), or cationically derivatized, hydrophilic PVDF; so bound, the polypeptides or fusion proteins of the present invention can be used to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized polypeptide or fusion protein of the present invention.

25 As another example, the polypeptides or fusion proteins of the present invention can usefully be bound to a substantially nonporous substrate, such as plastic, to detect and quantify antibodies, *e.g.* in serum, that bind specifically to the immobilized protein of the present invention. Such plastics include polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene, polycarbonate, polyacetal, polysulfone, celluloseacetate, cellulosenitrate, 30 nitrocellulose, or mixtures thereof; when the assay is performed in a standard microtiter dish, the plastic is typically polystyrene.

The polypeptides and fusion proteins of the present invention can also be attached to a substrate suitable for use as a surface enhanced laser desorption ionization source; so

attached, the polypeptide or fusion protein of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound polypeptide or fusion protein to indicate biologic interaction there between.

The polypeptides or fusion proteins of the present invention can also be attached to a

- 5 substrate suitable for use in surface plasmon resonance detection; so attached, the polypeptide or fusion protein of the present invention is useful for binding and then detecting secondary proteins that bind with sufficient affinity or avidity to the surface-bound polypeptide or fusion protein to indicate biological interaction there between.

Alternative Transcripts

10 In another aspect, the present invention provides splice variants of genes and proteins encoded thereby. The identification of a novel splice variant which encodes an amino acid sequence with a novel region can be targeted for the generation of reagents for use in detection and/or treatment of cancer. The novel amino acid sequence may lead to a unique protein structure, protein subcellular localization, biochemical processing or 15 function of the splice variant. This information can be used to directly or indirectly facilitate the generation of additional or novel therapeutics or diagnostics. The nucleotide sequence in this novel splice variant can be used as a nucleic acid probe for the diagnosis and/or treatment of cancer.

Specifically, the newly identified sequences may enable the production of new 20 antibodies or compounds directed against the novel region for use as a therapeutic or diagnostic. Alternatively, the newly identified sequences may alter the biochemical or biological properties of the encoded protein in such a way as to enable the generation of improved or different therapeutics targeting this protein.

Antibodies

25 In another aspect, the invention provides antibodies, including fragments and derivatives thereof, that bind specifically to polypeptides encoded by the nucleic acid molecules of the invention. In a preferred embodiment, the antibodies are specific for a polypeptide that is a BSP, or a fragment, mutein, derivative, analog or fusion protein thereof. In a more preferred embodiment, the antibodies are specific for a polypeptide that 30 comprises SEQ ID NO: 73-179, or a fragment, mutein, derivative, analog or fusion protein thereof.

The antibodies of the present invention can be specific for linear epitopes, discontinuous epitopes, or conformational epitopes of such proteins or protein fragments, either as present on the protein in its native conformation or, in some cases, as present on the proteins as denatured, as, e.g., by solubilization in SDS. New epitopes may also be
5 due to a difference in post translational modifications (PTMs) in disease versus normal tissue. For example, a particular site on a BSP may be glycosylated in cancerous cells, but not glycosylated in normal cells or vice versa. In addition, alternative splice forms of a
BSP may be indicative of cancer. Differential degradation of the C or N-terminus of a
BSP may also be a marker or target for anticancer therapy. For example, a BSP may be
10 N-terminal degraded in cancer cells exposing new epitopes to antibodies which may selectively bind for diagnostic or therapeutic uses.

As is well known in the art, the degree to which an antibody can discriminate among molecular species in a mixture will depend, in part, upon the conformational relatedness of the species in the mixture; typically, the antibodies of the present invention
15 will discriminate over adventitious binding to non-BSP polypeptides by at least two-fold, more typically by at least 5-fold, typically by more than 10-fold, 25-fold, 50-fold, 75-fold, and often by more than 100-fold, and on occasion by more than 500-fold or 1000-fold.
When used to detect the proteins or protein fragments of the present invention, the antibody of the present invention is sufficiently specific when it can be used to determine
20 the presence of the polypeptide of the present invention in samples derived from human breast.

Typically, the affinity or avidity of an antibody (or antibody multimer, as in the case of an IgM pentamer) of the present invention for a protein or protein fragment of the present invention will be at least about 1×10^{-6} molar (M), typically at least about 5×10^{-7}
25 M, 1×10^{-7} M, with affinities and avidities of at least 1×10^{-8} M, 5×10^{-9} M, 1×10^{-10} M and up to 1×10^{-13} M proving especially useful.

The antibodies of the present invention can be naturally occurring forms, such as IgG, IgM, IgD, IgE, IgY, and IgA, from any avian, reptilian, or mammalian species.

Human antibodies can, but will infrequently, be drawn directly from human donors
30 or human cells. In such case, antibodies to the polypeptides of the present invention will typically have resulted from fortuitous immunization, such as autoimmune immunization, with the polypeptide of the present invention. Such antibodies will typically, but will not

invariably, be polyclonal. In addition, individual polyclonal antibodies may be isolated and cloned to generate monoclonals.

Human antibodies are more frequently obtained using transgenic animals that express human immunoglobulin genes, which transgenic animals can be affirmatively 5 immunized with the protein immunogen of the present invention. Human Ig-transgenic mice capable of producing human antibodies and methods of producing human antibodies therefrom upon specific immunization are described, *inter alia*, in U.S. Patent Nos. 6,162,963; 6,150,584; 6,114,598; 6,075,181; 5,939,598; 5,877,397; 5,874,299; 5,814,318; 5,789,650; 5,770,429; 5,661,016; 5,633,425; 5,625,126; 5,569,825; 5,545,807; 5,545,806, 10 and 5,591,669, the disclosures of which are incorporated herein by reference in their entireties. Such antibodies are typically monoclonal, and are typically produced using techniques developed for production of murine antibodies.

Human antibodies are particularly useful, and often preferred, when the antibodies 15 of the present invention are to be administered to human beings as *in vivo* diagnostic or therapeutic agents, since recipient immune response to the administered antibody will often be substantially less than that occasioned by administration of an antibody derived from another species, such as mouse.

IgG, IgM, IgD, IgE, IgY, and IgA antibodies of the present invention are also 20 usefully obtained from other species, including mammals such as rodents (typically mouse, but also rat, guinea pig, and hamster), lagomorphs (typically rabbits), and also larger mammals, such as sheep, goats, cows, and horses; or egg laying birds or reptiles such as chickens or alligators. In such cases, as with the transgenic human-antibody-producing non-human mammals, fortuitous immunization is not required, and the non-human mammal is typically affirmatively immunized, according to standard immunization 25 protocols, with the polypeptide of the present invention. One form of avian antibodies may be generated using techniques described in WO 00/29444, published 25 May 2000, which is herein incorporated by reference in its entirety.

As discussed above, virtually all fragments of 8 or more contiguous amino acids of 30 a polypeptide of the present invention can be used effectively as immunogens when conjugated to a carrier, typically a protein such as bovine thyroglobulin, keyhole limpet hemocyanin, or bovine serum albumin, conveniently using a bifunctional linker such as those described elsewhere above, which discussion is incorporated by reference here.

Immunogenicity can also be conferred by fusion of the polypeptides of the present invention to other moieties. For example, polypeptides of the present invention can be produced by solid phase synthesis on a branched polylysine core matrix; these multiple antigenic peptides (MAPs) provide high purity, increased avidity, accurate chemical definition and improved safety in vaccine development. Tam *et al.*, *Proc. Natl. Acad. Sci. USA* 85: 5409-5413 (1988); Posnett *et al.*, *J. Biol. Chem.* 263: 1719-1725 (1988).

Protocols for immunizing non-human mammals or avian species are well-established in the art. See Harlow *et al.* (eds.), Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory (1998); Coligan *et al.* (eds.), Current Protocols in Immunology, John Wiley & Sons, Inc. (2001); Zola, Monoclonal Antibodies: Preparation and Use of Monoclonal Antibodies and Engineered Antibody Derivatives (Basics: From Background to Bench), Springer Verlag (2000); Gross M, Speck *J.Dtsch. Tierarztl. Wochenschr.* 103: 417-422 (1996). Immunization protocols often include multiple immunizations, either with or without adjuvants such as Freund's complete adjuvant and Freund's incomplete adjuvant, and may include naked DNA immunization. Moss, *Semin. Immunol.* 2: 317-327 (1990).

Antibodies from non-human mammals and avian species can be polyclonal or monoclonal, with polyclonal antibodies having certain advantages in immunohistochemical detection of the polypeptides of the present invention and monoclonal antibodies having advantages in identifying and distinguishing particular epitopes of the polypeptides of the present invention. Antibodies from avian species may have particular advantage in detection of the polypeptides of the present invention, in human serum or tissues. Vikinge *et al.*, *Biosens. Bioelectron.* 13: 1257-1262 (1998). Following immunization, the antibodies of the present invention can be obtained using any art-accepted technique. Such techniques are well known in the art and are described in detail in references such as Coligan, *supra*; Zola, *supra*; Howard *et al.* (eds.), Basic Methods in Antibody Production and Characterization, CRC Press (2000); Harlow, *supra*; Davis (ed.), Monoclonal Antibody Protocols, Vol. 45, Humana Press (1995); Delves (ed.), Antibody Production: Essential Techniques, John Wiley & Son Ltd (1997); and Kenney, Antibody Solution: An Antibody Methods Manual, Chapman & Hall (1997).

Briefly, such techniques include, *inter alia*, production of monoclonal antibodies by hybridomas and expression of antibodies or fragments or derivatives thereof from host cells engineered to express immunoglobulin genes or fragments thereof. These two

methods of production are not mutually exclusive: genes encoding antibodies specific for the polypeptides of the present invention can be cloned from hybridomas and thereafter expressed in other host cells. Nor need the two necessarily be performed together: e.g., genes encoding antibodies specific for the polypeptides of the present invention can be 5 cloned directly from B cells known to be specific for the desired protein, as further described in U.S. Patent No. 5,627,052, the disclosure of which is incorporated herein by reference in its entirety, or from antibody-displaying phage.

Recombinant expression in host cells is particularly useful when fragments or derivatives of the antibodies of the present invention are desired.

10 Host cells for recombinant antibody production of whole antibodies, antibody fragments, or antibody derivatives can be prokaryotic or eukaryotic.

Prokaryotic hosts are particularly useful for producing phage displayed antibodies of the present invention.

15 The technology of phage-displayed antibodies, in which antibody variable region fragments are fused, for example, to the gene III protein (pIII) or gene VIII protein (pVIII) for display on the surface of filamentous phage, such as M13, is by now well-established. See, e.g., Sidhu, *Curr. Opin. Biotechnol.* 11(6): 610-6 (2000); Griffiths *et al.*, *Curr. Opin. Biotechnol.* 9(1): 102-8 (1998); Hoogenboom *et al.*, *Immunotechnology*, 4(1): 1-20 (1998); Rader *et al.*, *Current Opinion in Biotechnology* 8: 503-508 (1997); Aujame *et al.*, *Human Antibodies* 8: 155-168 (1997); Hoogenboom, *Trends in Biotechnol.* 15: 62-70 (1997); de 20 Kruif *et al.*, 17: 453-455 (1996); Barbas *et al.*, *Trends in Biotechnol.* 14: 230-234 (1996); Winter *et al.*, *Ann. Rev. Immunol.* 433-455 (1994). Techniques and protocols required to generate, propagate, screen (pan), and use the antibody fragments from such libraries have recently been compiled. See, e.g., Barbas (2001), *supra*; Kay, *supra*; and Abelson, *supra*.

25 Typically, phage-displayed antibody fragments are scFv fragments or Fab fragments; when desired, full length antibodies can be produced by cloning the variable regions from the displaying phage into a complete antibody and expressing the full length antibody in a further prokaryotic or a eukaryotic host cell. Eukaryotic cells are also useful for expression of the antibodies, antibody fragments, and antibody derivatives of the 30 present invention. For example, antibody fragments of the present invention can be produced in *Pichia pastoris* and in *Saccharomyces cerevisiae*. See, e.g., Takahashi *et al.*, *Biosci. Biotechnol. Biochem.* 64(10): 2138-44 (2000); Freyre *et al.*, *J. Biotechnol.* 76(2-3): 1 57-63 (2000); Fischer *et al.*, *Biotechnol. Appl. Biochem.* 30 (Pt 2): 117-20

(1999); Pennell *et al.*, *Res. Immunol.* 149(6): 599-603 (1998); Eldin *et al.*, *J. Immunol. Methods.* 201(1): 67-75 (1997);, Frenken *et al.*, *Res. Immunol.* 149(6): 589-99 (1998); and Shusta *et al.*, *Nature Biotechnol.* 16(8): 773-7 (1998).

Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in insect cells. See, e.g., Li *et al.*, *Protein Expr. Purif.* 21(1): 121-8 (2001); Ailor *et al.*, *Biotechnol. Bioeng.* 58(2-3): 196-203 (1998); Hsu *et al.*, *Biotechnol. Prog.* 13(1): 96-104 (1997); Edelman *et al.*, *Immunology* 91(1): 13-9 (1997); and Nesbit *et al.*, *J. Immunol. Methods* 151(1-2): 201-8 (1992).

Antibodies and fragments and derivatives thereof of the present invention can also be produced in plant cells, particularly maize or tobacco, Giddings *et al.*, *Nature Biotechnol.* 18(11): 1151-5 (2000); Gavilondo *et al.*, *Biotechniques* 29(1): 128-38 (2000); Fischer *et al.*, *J. Biol. Regul. Homeost. Agents* 14(2): 83-92 (2000); Fischer *et al.*, *Biotechnol. Appl. Biochem.* 30 (Pt 2): 113-6 (1999); Fischer *et al.*, *Biol. Chem.* 380(7-8): 825-39 (1999); Russell, *Curr. Top. Microbiol. Immunol.* 240: 119-38 (1999); and Ma *et al.*, *Plant Physiol.* 109(2): 341-6 (1995).

Antibodies, including antibody fragments and derivatives, of the present invention can also be produced in transgenic, non-human, mammalian milk. See, e.g. Pollock *et al.*, *J. Immunol Methods.* 231: 147-57 (1999); Young *et al.*, *Res. Immunol.* 149: 609-10 (1998); and Limonta *et al.*, *Immunotechnology* 1: 107-13 (1995).

Mammalian cells useful for recombinant expression of antibodies, antibody fragments, and antibody derivatives of the present invention include CHO cells, COS cells, 293 cells, and myeloma cells. Verma *et al.*, *J. Immunol. Methods* 216(1-2):165-81 (1998) review and compare bacterial, yeast, insect and mammalian expression systems for expression of antibodies. Antibodies of the present invention can also be prepared by cell free translation, as further described in Merk *et al.*, *J. Biochem.* (Tokyo) 125(2): 328-33 (1999) and Ryabova *et al.*, *Nature Biotechnol.* 15(1): 79-84 (1997), and in the milk of transgenic animals, as further described in Pollock *et al.*, *J. Immunol. Methods* 231(1-2): 147-57 (1999).

The invention further provides antibody fragments that bind specifically to one or more of the polypeptides of the present invention or to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid

molecules of the present invention. Among such useful fragments are Fab, Fab', Fv, F(ab)'₂, and single chain Fv (scFv) fragments. Other useful fragments are described in Hudson, *Curr. Opin. Biotechnol.* 9(4): 395-402 (1998).

The present invention also relates to antibody derivatives that bind specifically to
5 one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention.

10 Among such useful derivatives are chimeric, primatized, and humanized antibodies; such derivatives are less immunogenic in human beings, and thus are more suitable for *in vivo* administration, than are unmodified antibodies from non-human mammalian species. Another useful method is PEGylation to increase the serum half life of the antibodies.

15 Chimeric antibodies typically include heavy and/or light chain variable regions (including both CDR and framework residues) of immunoglobulins of one species, typically mouse, fused to constant regions of another species, typically human. See, e.g., Morrison *et al.*, *Proc. Natl. Acad. Sci USA* 81(21): 6851-5 (1984); Sharon *et al.*, *Nature* 309(5966): 364-7 (1984); Takeda *et al.*, *Nature* 314(6010): 452-4 (1985); and U.S. Patent
20 No. 5,807,715 the disclosure of which is incorporated herein by reference in its entirety. Primatized and humanized antibodies typically include heavy and/or light chain CDRs from a murine antibody grafted into a non-human primate or human antibody V region framework, usually further comprising a human constant region, Riechmann *et al.*, *Nature* 332(6162): 323-7 (1988); Co *et al.*, *Nature* 351(6326): 501-2 (1991); and U.S. Patent Nos.
25 6,054,297; 5,821,337; 5,770,196; 5,766,886; 5,821,123; 5,869,619; 6,180,377; 6,013,256; 5,693,761; and 6,180,370, the disclosures of which are incorporated herein by reference in their entireties. Other useful antibody derivatives of the invention include heteromeric antibody complexes and antibody fusions, such as diabodies (bispecific antibodies), single-chain diabodies, and intrabodies.

30 It is contemplated that the nucleic acids encoding the antibodies of the present invention can be operably joined to other nucleic acids forming a recombinant vector for cloning or for expression of the antibodies of the invention. Accordingly, the present invention includes any recombinant vector containing the coding sequences, or part

thereof, whether for eukaryotic transduction, transfection or gene therapy. Such vectors may be prepared using conventional molecular biology techniques, known to those with skill in the art, and would comprise DNA encoding sequences for the immunoglobulin V-regions including framework and CDRs or parts thereof, and a suitable promoter either

- 5 with or without a signal sequence for intracellular transport. Such vectors may be transduced or transfected into eukaryotic cells or used for gene therapy (Marasco et al., *Proc. Natl. Acad. Sci. (USA)* 90: 7889-7893 (1993); Duan et al., *Proc. Natl. Acad. Sci. (USA)* 91: 5075-5079 (1994), by conventional techniques, known to those with skill in the art.

- 10 The antibodies of the present invention, including fragments and derivatives thereof, can usefully be labeled. It is, therefore, another aspect of the present invention to provide labeled antibodies that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited
15 by one or more of the polypeptides of the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention. The choice of label depends, in part, upon the desired use.

For example, when the antibodies of the present invention are used for immunohistochemical staining of tissue samples, the label can usefully be an enzyme that
20 catalyzes production and local deposition of a detectable product. Enzymes typically conjugated to antibodies to permit their immunohistochemical visualization are well known, and include alkaline phosphatase, β -galactosidase, glucose oxidase, horseradish peroxidase (HRP), and urease. Typical substrates for production and deposition of visually detectable products include o-nitrophenyl-beta-D-galactopyranoside (ONPG);
25 o-phenylenediamine dihydrochloride (OPD); p-nitrophenyl phosphate (PNPP); p-nitrophenyl-beta-D-galactopyranoside (PNPG); 3',3'-diaminobenzidine (DAB); 3-amino-9-ethylcarbazole (AEC); 4-chloro-1-naphthol (CN);
5-bromo-4-chloro-3-indolyl-phosphate (BCIP); ABTS®; Bluogal; iodonitrotetrazolium (INT); nitroblue tetrazolium chloride (NBT); phenazine methosulfate (PMS);
30 phenolphthalein monophosphate (PMP); tetramethyl benzidine (TMB); tetranitroblue tetrazolium (TNBT); X-Gal; X-Gluc; and X-Glucoside.

Other substrates can be used to produce products for local deposition that are luminescent. For example, in the presence of hydrogen peroxide (H_2O_2), horseradish

peroxidase (HRP) can catalyze the oxidation of cyclic diacylhydrazides, such as luminol. Immediately following the oxidation, the luminol is in an excited state (intermediate reaction product), which decays to the ground state by emitting light. Strong enhancement of the light emission is produced by enhancers, such as phenolic compounds. Advantages 5 include high sensitivity, high resolution, and rapid detection without radioactivity and requiring only small amounts of antibody. See, e.g., Thorpe *et al.*, *Methods Enzymol.* 133: 331-53 (1986); Kricka *et al.*, *J. Immunoassay* 17(1): 67-83 (1996); and Lundqvist *et al.*, *J. Biolumin. Chemilumin.* 10(6): 353-9 (1995). Kits for such enhanced chemiluminescent detection (ECL) are available commercially. The antibodies can also be labeled using 10 colloidal gold.

As another example, when the antibodies of the present invention are used, e.g., for flow cytometric detection, for scanning laser cytometric detection, or for fluorescent immunoassay, they can usefully be labeled with fluorophores. There are a wide variety of fluorophore labels that can usefully be attached to the antibodies of the present invention. 15 For flow cytometric applications, both for extracellular detection and for intracellular detection, common useful fluorophores can be fluorescein isothiocyanate (FITC), allophycocyanin (APC), R-phycoerythrin (PE), peridinin chlorophyll protein (PerCP), Texas Red, Cy3, Cy5, fluorescence resonance energy tandem fluorophores such as PerCP-Cy5.5, PE-Cy5, PE-Cy5.5, PE-Cy7, PE-Texas Red, and APC-Cy7.

Other fluorophores include, *inter alia*, Alexa Fluor® 350, Alexa Fluor® 488, 20 Alexa Fluor® 532, Alexa Fluor® 546, Alexa Fluor® 568, Alexa Fluor® 594, Alexa Fluor® 647 (monoclonal antibody labeling kits available from Molecular Probes, Inc., Eugene, OR, USA), BODIPY dyes, such as BODIPY 493/503, BODIPY FL, BODIPY R6G, BODIPY 530/550, BODIPY TMR, BODIPY 558/568, BODIPY 558/568, BODIPY 25 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY TR, BODIPY 630/650, BODIPY 650/665, Cascade Blue, Cascade Yellow, Dansyl, lissamine rhodamine B, Marina Blue, Oregon Green 488, Oregon Green 514, Pacific Blue, rhodamine 6G, rhodamine green, rhodamine red, tetramethylrhodamine, Texas Red (available from 30 Molecular Probes, Inc., Eugene, OR, USA), and Cy2, Cy3, Cy3.5, Cy5, Cy5.5, Cy7, all of which are also useful for fluorescently labeling the antibodies of the present invention. For secondary detection using labeled avidin, streptavidin, captavidin or neutravidin, the antibodies of the present invention can usefully be labeled with biotin.

When the antibodies of the present invention are used, *e.g.*, for western blotting applications, they can usefully be labeled with radioisotopes, such as ^{33}P , ^{32}P , ^{35}S , ^3H , and ^{125}I . As another example, when the antibodies of the present invention are used for radioimmunotherapy, the label can usefully be ^{228}Th , ^{227}Ac , ^{225}Ac , ^{223}Ra , ^{213}Bi , ^{212}Pb ,
5 ^{212}Bi , ^{211}At , ^{203}Pb , ^{194}Os , ^{188}Re , ^{186}Re , ^{153}Sm , ^{149}Tb , ^{131}I , ^{125}I , ^{111}In , ^{105}Rh , $^{99\text{m}}\text{Tc}$, ^{97}Ru , ^{90}Y ,
 ^{90}Sr , ^{88}Y , ^{72}Se , ^{67}Cu , or ^{47}Sc .

As another example, when the antibodies of the present invention are to be used for *in vivo* diagnostic use, they can be rendered detectable by conjugation to MRI contrast agents, such as gadolinium diethylenetriaminepentaacetic acid (DTPA), Lauffer *et al.*,
10 *Radiology* 207(2): 529-38 (1998), or by radioisotopic labeling.

As would be understood, use of the labels described above is not restricted to the application as for which they were mentioned.

The antibodies of the present invention, including fragments and derivatives thereof, can also be conjugated to toxins, in order to target the toxin's ablative action to
15 cells that display and/or express the polypeptides of the present invention. Commonly, the antibody in such immunotoxins is conjugated to Pseudomonas exotoxin A, diphtheria toxin, shiga toxin A, anthrax toxin lethal factor, or ricin. See Hall (ed.), Immunotoxin Methods and Protocols (Methods in Molecular Biology, vol. 166), Humana Press (2000); and Frankel *et al.* (eds.), Clinical Applications of Immunotoxins, Springer-Verlag (1998).

20 The antibodies of the present invention can usefully be attached to a substrate, and it is, therefore, another aspect of the invention to provide antibodies that bind specifically to one or more of the polypeptides of the present invention, to one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, or the binding of which can be competitively inhibited by one or more of the polypeptides of
25 the present invention or one or more of the polypeptides encoded by the isolated nucleic acid molecules of the present invention, attached to a substrate. Substrates can be porous or nonporous, planar or nonplanar. For example, the antibodies of the present invention can usefully be conjugated to filtration media, such as NHS-activated Sepharose or CNBr-activated Sepharose for purposes of immunoaffinity chromatography. For example, the
30 antibodies of the present invention can usefully be attached to paramagnetic microspheres, typically by biotin-streptavidin interaction, which microsphere can then be used for isolation of cells that express or display the polypeptides of the present invention. As

another example, the antibodies of the present invention can usefully be attached to the surface of a microtiter plate for ELISA.

As noted above, the antibodies of the present invention can be produced in prokaryotic and eukaryotic cells. It is, therefore, another aspect of the present invention to provide cells that express the antibodies of the present invention, including hybridoma cells, B cells, plasma cells, and host cells recombinantly modified to express the antibodies of the present invention.

In yet a further aspect, the present invention provides aptamers evolved to bind specifically to one or more of the BSPs of the present invention or to polypeptides encoded by the BSNA^s of the invention.

In sum, one of skill in the art, provided with the teachings of this invention, has available a variety of methods which may be used to alter the biological properties of the antibodies of this invention including methods which would increase or decrease the stability or half-life, immunogenicity, toxicity, affinity or yield of a given antibody molecule, or to alter it in any other way that may render it more suitable for a particular application.

Transgenic Animals and Cells

In another aspect, the invention provides transgenic cells and non-human organisms comprising nucleic acid molecules of the invention. In a preferred embodiment, the transgenic cells and non-human organisms comprise a nucleic acid molecule encoding a BSP. In a preferred embodiment, the BSP comprises an amino acid sequence selected from SEQ ID NO: 73-179, or a fragment, mutein, homologous protein or allelic variant thereof. In another preferred embodiment, the transgenic cells and non-human organism comprise a BSNA of the invention, preferably a BSNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-72, or a part, substantially similar nucleic acid molecule, allelic variant or hybridizing nucleic acid molecule thereof.

In another embodiment, the transgenic cells and non-human organisms have a targeted disruption or replacement of the endogenous orthologue of the human BSG. The transgenic cells can be embryonic stem cells or somatic cells. The transgenic non-human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes. Methods of producing transgenic animals are well known in the art. *See, e.g., Hogan et*

et al., Manipulating the Mouse Embryo: A Laboratory Manual, 2d ed., Cold Spring Harbor Press (1999); Jackson *et al.*, Mouse Genetics and Transgenics: A Practical Approach, Oxford University Press (2000); and Pinkert, Transgenic Animal Technology: A Laboratory Handbook, Academic Press (1999).

5 Any technique known in the art may be used to introduce a nucleic acid molecule of the invention into an animal to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection. (*see, e.g.*, Paterson *et al.*, *Appl. Microbiol. Biotechnol.* 40: 691-698 (1994); Carver *et al.*, *Biotechnology* 11: 1263-1270 (1993); Wright *et al.*, *Biotechnology* 9: 830-834 (1991); and U.S. Patent No. 10 4,873,191, herein incorporated by reference in its entirety); retrovirus-mediated gene transfer into germ lines, blastocysts or embryos (*see, e.g.*, Van der Putten *et al.*, *Proc. Natl. Acad. Sci., USA* 82: 6148-6152 (1985)); gene targeting in embryonic stem cells (*see, e.g.*, Thompson *et al.*, *Cell* 56: 313-321 (1989)); electroporation of cells or embryos (*see, e.g.*, Lo, 1983, *Mol. Cell. Biol.* 3: 1803-1814 (1983)); introduction using a gene gun (*see, e.g.*, Ulmer *et al.*, *Science* 259: 1745-49 (1993)); introducing nucleic acid constructs into 15 embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (*see, e.g.*, Lavitrano *et al.*, *Cell* 57: 717-723 (1989)).

Other techniques include, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (*see, e.g.*, 20 Campell *et al.*, *Nature* 380: 64-66 (1996); Wilmut *et al.*, *Nature* 385: 810-813 (1997)). The present invention provides for transgenic animals that carry the transgene (*i.e.*, a nucleic acid molecule of the invention) in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.* e., mosaic animals or chimeric animals.

The transgene may be integrated as a single transgene or as multiple copies, such 25 as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, *e.g.*, the teaching of Lasko *et al.* *et al.*, *Proc. Natl. Acad. Sci. USA* 89: 6232- 6236 (1992). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

30 Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the

transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (RT-PCR).

Samples of transgenic gene-expressing tissue may also be evaluated

- 5 immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than 10 one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Methods for creating a transgenic animal with a disruption of a targeted gene are also well known in the art. In general, a vector is designed to comprise some nucleotide sequences homologous to the endogenous targeted gene. The vector is introduced into a cell so that it may integrate, via homologous recombination with chromosomal sequences, into the endogenous gene, thereby disrupting the function of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type. *See, e.g., Gu et al., Science 265: 103-106 (1994).* The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. *See, e.g., Smithies et al., Nature 317: 230-234 (1985); Thomas et al., Cell 51: 503-512 (1987); Thompson et al., Cell 5: 313-321 (1989).*

- In one embodiment, a mutant, non-functional nucleic acid molecule of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous nucleic acid sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable
- 5 marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications
- 10 to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene. *See, e.g., Thomas, supra* and *Thompson, supra*. However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.
- 15 In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.,* knockouts) are administered to a patient *in vivo*. Such cells may be obtained from an animal or patient or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells,
- 20 blood cells (*e.g.,* lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.,* by transduction (using viral vectors, and preferably
- 25 vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve

30 expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.,* in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. *See, e.g.*, U.S. Patent Nos. 5,399,349 and 5,460,959, each of which is 5 incorporated by reference herein in its entirety.

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the 10 cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with 15 aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Computer Readable Means

A further aspect of the invention is a computer readable means for storing the 20 nucleic acid and amino acid sequences of the instant invention. In a preferred embodiment, the invention provides a computer readable means for storing SEQ ID NO: 73-179 and SEQ ID NO: 1-72 as described herein, as the complete set of sequences or in any combination. The records of the computer readable means can be accessed for reading and display and for interface with a computer system for the application of programs allowing for the location of data upon a query for data meeting certain criteria, 25 the comparison of sequences, the alignment or ordering of sequences meeting a set of criteria, and the like.

The nucleic acid and amino acid sequences of the invention are particularly useful as components in databases useful for search analyses as well as in sequence analysis algorithms. As used herein, the terms "nucleic acid sequences of the invention" and 30 "amino acid sequences of the invention" mean any detectable chemical or physical characteristic of a polynucleotide or polypeptide of the invention that is or may be reduced to or stored in a computer readable form. These include, without limitation,

chromatographic scan data or peak data, photographic data or scan data therefrom, and mass spectrographic data.

This invention provides computer readable media having stored thereon sequences of the invention. A computer readable medium may comprise one or more of the following:

5 a nucleic acid sequence comprising a sequence of a nucleic acid sequence of the invention; an amino acid sequence comprising an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said sequences comprises the sequence of a nucleic acid sequence of the invention; a set of amino acid sequences wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention;

10 a data set representing a nucleic acid sequence comprising the sequence of one or more nucleic acid sequences of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention; a set of nucleic acid sequences wherein at least one of said sequences comprises the sequence of a nucleic acid sequence of the invention; a set of

15 amino acid sequences wherein at least one of said sequences comprises the sequence of an amino acid sequence of the invention; a data set representing a nucleic acid sequence comprising the sequence of a nucleic acid sequence of the invention; a data set representing a nucleic acid sequence encoding an amino acid sequence comprising the sequence of an amino acid sequence of the invention. The computer readable medium can

20 be any composition of matter used to store information or data, including, for example, commercially available floppy disks, tapes, hard drives, compact disks, and video disks.

Also provided by the invention are methods for the analysis of character sequences, particularly genetic sequences. Preferred methods of sequence analysis include, for example, methods of sequence homology analysis, such as identity and

25 similarity analysis, RNA structure analysis, sequence assembly, cladistic analysis, sequence motif analysis, open reading frame determination, nucleic acid base calling, and sequencing chromatogram peak analysis.

A computer-based method is provided for performing nucleic acid sequence identity or similarity identification. This method comprises the steps of providing a

30 nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and comparing said nucleic acid sequence to at least one nucleic acid or amino acid sequence to identify sequence identity or similarity.

A computer-based method is also provided for performing amino acid homology identification, said method comprising the steps of: providing an amino acid sequence comprising the sequence of an amino acid of the invention in a computer readable medium; and comparing said amino acid sequence to at least one nucleic acid or an amino acid sequence to identify homology.

A computer-based method is still further provided for assembly of overlapping nucleic acid sequences into a single nucleic acid sequence, said method comprising the steps of: providing a first nucleic acid sequence comprising the sequence of a nucleic acid of the invention in a computer readable medium; and screening for at least one overlapping region between said first nucleic acid sequence and a second nucleic acid sequence. In addition, the invention includes a method of using patterns of expression associated with either the nucleic acids or proteins in a computer-based method to diagnose disease.

Diagnostic Methods for Breast Cancer

The present invention also relates to quantitative and qualitative diagnostic assays and methods for detecting, diagnosing, monitoring, staging and predicting cancers by comparing expression of a BSNA or a BSP in a human patient that has or may have breast cancer, or who is at risk of developing breast cancer, with the expression of a BSNA or a BSP in a normal human control. For purposes of the present invention, "expression of a BSNA" or "BSNA expression" means the quantity of BSNA mRNA that can be measured by any method known in the art or the level of transcription that can be measured by any method known in the art in a cell, tissue, organ or whole patient. Similarly, the term "expression of a BSP" or "BSP expression" means the amount of BSP that can be measured by any method known in the art or the level of translation of a BSNA that can be measured by any method known in the art.

The present invention provides methods for diagnosing breast cancer in a patient, by analyzing for changes in levels of BSNA or BSP in cells, tissues, organs or bodily fluids compared with levels of BSNA or BSP in cells, tissues, organs or bodily fluids of preferably the same type from a normal human control, wherein an increase, or decrease in certain cases, in levels of a BSNA or BSP in the patient versus the normal human control is associated with the presence of breast cancer or with a predilection to the disease. In another preferred embodiment, the present invention provides methods for diagnosing

breast cancer in a patient by analyzing changes in the structure of the mRNA of a BSG compared to the mRNA from a normal control. These changes include, without limitation, aberrant splicing, alterations in polyadenylation and/or alterations in 5' nucleotide capping. In yet another preferred embodiment, the present invention provides methods for 5 diagnosing breast cancer in a patient by analyzing changes in a BSP compared to a BSP from a normal patient. These changes include, *e.g.*, alterations, including post translational modifications such as glycosylation and/or phosphorylation of the BSP or changes in the subcellular BSP localization.

For purposes of the present invention, diagnosing means that BSNA or BSP levels 10 are used to determine the presence or absence of disease in a patient. As will be understood by those of skill in the art, measurement of other diagnostic parameters may be required for definitive diagnosis or determination of the appropriate treatment for the disease. The determination may be made by a clinician, a doctor, a testing laboratory, or a patient using an over the counter test. The patient may have symptoms of disease or may 15 be asymptomatic. In addition, the BSNA or BSP levels of the present invention may be used as screening marker to determine whether further tests or biopsies are warranted. In addition, the BSNA or BSP levels may be used to determine the vulnerability or susceptibility to disease.

In a preferred embodiment, the expression of a BSNA is measured by determining 20 the amount of a mRNA that encodes an amino acid sequence selected from SEQ ID NO: 73-179, a homolog, an allelic variant, or a fragment thereof. In a more preferred embodiment, the BSNA expression that is measured is the level of expression of a BSNA mRNA selected from SEQ ID NO: 1-72, or a hybridizing nucleic acid, homologous nucleic acid or allelic variant thereof, or a part of any of these nucleic acid molecules. 25 BSNA expression may be measured by any method known in the art, such as those described *supra*, including measuring mRNA expression by Northern blot, quantitative or qualitative reverse transcriptase PCR (RT-PCR), microarray, dot or slot blots or *in situ* hybridization. *See, e.g.*, Ausubel (1992), *supra*; Ausubel (1999), *supra*; Sambrook (1989), *supra*; and Sambrook (2001), *supra*. BSNA transcription may be measured by any 30 method known in the art including using a reporter gene hooked up to the promoter of a BSG of interest or doing nuclear run-off assays. Alterations in mRNA structure, *e.g.*, aberrant splicing variants, may be determined by any method known in the art, including, RT-PCR followed by sequencing or restriction analysis. As necessary, BSNA expression

may be compared to a known control, such as normal breast nucleic acid, to detect a change in expression.

In another preferred embodiment, the expression of a BSP is measured by determining the level of a BSP having an amino acid sequence selected from the group consisting of SEQ ID NO: 73-179, a homolog, an allelic variant, or a fragment thereof. Such levels are preferably determined in at least one of cells, tissues, organs and/or bodily fluids, including determination of normal and abnormal levels. Thus, for instance, a diagnostic assay in accordance with the invention for diagnosing over- or underexpression of a BSNA or BSP compared to normal control bodily fluids, cells, or tissue samples may be used to diagnose the presence of breast cancer. The expression level of a BSP may be determined by any method known in the art, such as those described *supra*. In a preferred embodiment, the BSP expression level may be determined by radioimmunoassays, competitive-binding assays, ELISA, Western blot, FACS, immunohistochemistry, immunoprecipitation, proteomic approaches: two-dimensional gel electrophoresis (2D electrophoresis) and non-gel-based approaches such as mass spectrometry or protein interaction profiling. *See, e.g.*, Harlow (1999), *supra*; Ausubel (1992), *supra*; and Ausubel (1999), *supra*. Alterations in the BSP structure may be determined by any method known in the art, including, *e.g.*, using antibodies that specifically recognize phosphoserine, phosphothreonine or phosphotyrosine residues, two-dimensional polyacrylamide gel electrophoresis (2D PAGE) and/or chemical analysis of amino acid residues of the protein. *Id.*

In a preferred embodiment, a radioimmunoassay (RIA) or an ELISA is used. An antibody specific to a BSP is prepared if one is not already available. In a preferred embodiment, the antibody is a monoclonal antibody. The anti-BSP antibody is bound to a solid support and any free protein binding sites on the solid support are blocked with a protein such as bovine serum albumin. A sample of interest is incubated with the antibody on the solid support under conditions in which the BSP will bind to the anti-BSP antibody. The sample is removed, the solid support is washed to remove unbound material, and an anti-BSP antibody that is linked to a detectable reagent (a radioactive substance for RIA and an enzyme for ELISA) is added to the solid support and incubated under conditions in which binding of the BSP to the labeled antibody will occur. After binding, the unbound labeled antibody is removed by washing. For an ELISA, one or more substrates are added to produce a colored reaction product that is based upon the amount of a BSP in the

sample. For an RIA, the solid support is counted for radioactive decay signals by any method known in the art. Quantitative results for both RIA and ELISA typically are obtained by reference to a standard curve.

Other methods to measure BSP levels are known in the art. For instance, a 5 competition assay may be employed wherein an anti-BSP antibody is attached to a solid support and an allocated amount of a labeled BSP and a sample of interest are incubated with the solid support. The amount of labeled BSP attached to the solid support can be correlated to the quantity of a BSP in the sample.

Of the proteomic approaches, 2D PAGE is a well known technique. Isolation of 10 individual proteins from a sample such as serum is accomplished using sequential separation of proteins by isoelectric point and molecular weight. Typically, polypeptides are first separated by isoelectric point (the first dimension) and then separated by size using an electric current (the second dimension). In general, the second dimension is perpendicular to the first dimension. Because no two proteins with different sequences are 15 identical on the basis of both size and charge, the result of 2D PAGE is a roughly square gel in which each protein occupies a unique spot. Analysis of the spots with chemical or antibody probes, or subsequent protein microsequencing can reveal the relative abundance of a given protein and the identity of the proteins in the sample.

Expression levels of a BSNA can be determined by any method known in the art, 20 including PCR and other nucleic acid methods, such as ligase chain reaction (LCR) and nucleic acid sequence based amplification (NASBA), can be used to detect malignant cells for diagnosis and monitoring of various malignancies. For example, reverse-transcriptase PCR (RT-PCR) is a powerful technique which can be used to detect the presence of a specific mRNA population in a complex mixture of thousands of other mRNA species. In 25 RT-PCR, an mRNA species is first reverse transcribed to complementary DNA (cDNA) with use of the enzyme reverse transcriptase; the cDNA is then amplified as in a standard PCR reaction.

Hybridization to specific DNA molecules (*e.g.*, oligonucleotides) arrayed on a solid support can be used to both detect the expression of and quantitate the level of 30 expression of one or more BSNA of interest. In this approach, all or a portion of one or more BSNA is fixed to a substrate. A sample of interest, which may comprise RNA, *e.g.*, total RNA or polyA-selected mRNA, or a complementary DNA (cDNA) copy of the RNA is incubated with the solid support under conditions in which hybridization will occur

between the DNA on the solid support and the nucleic acid molecules in the sample of interest. Hybridization between the substrate-bound DNA and the nucleic acid molecules in the sample can be detected and quantitated by several means, including, without limitation, radioactive labeling or fluorescent labeling of the nucleic acid molecule or a secondary molecule designed to detect the hybrid.

The above tests can be carried out on samples derived from a variety of cells, bodily fluids and/or tissue extracts such as homogenates or solubilized tissue obtained from a patient. Tissue extracts are obtained routinely from tissue biopsy and autopsy material. Bodily fluids useful in the present invention include blood, urine, saliva or any other bodily secretion or derivative thereof. As used herein "blood" includes whole blood, plasma, serum, circulating epithelial cells, constituents, or any derivative of blood.

In addition to detection in bodily fluids, the proteins and nucleic acids of the invention are suitable to detection by cell capture technology. Whole cells may be captured by a variety methods for example magnetic separation, such as described in U.S. Patent. Nos. 5,200,084; 5,186,827; 5,108,933; and 4,925,788, the disclosures of which are incorporated herein by reference in their entireties. Epithelial cells may be captured using such products as Dynabeads® or CELLlection™ (Dynal Biotech, Oslo, Norway). Alternatively, fractions of blood may be captured, e.g., the buffy coat fraction (50mm cells isolated from 5ml of blood) containing epithelial cells. In addition, cancer cells may be captured using the techniques described in WO 00/47998, the disclosure of which is incorporated herein by reference in its entirety. Once the cells are captured or concentrated, the proteins or nucleic acids are detected by the means described in the subject application. Alternatively, nucleic acids may be captured directly from blood samples, see U.S. Patent Nos. 6,156,504, 5,501,963; or WO 01/42504, the disclosures of which are incorporated herein by reference in their entireties.

In a preferred embodiment, the specimen tested for expression of BSNA or BSP includes without limitation breast tissue, breast cells grown in cell culture, blood, serum, lymph node tissue, and lymphatic fluid. In another preferred embodiment, especially when metastasis of a primary breast cancer is known or suspected, specimens include, without limitation, tissues from brain, bone, bone marrow, liver, lungs, colon, and adrenal glands. In general, the tissues may be sampled by biopsy, including, without limitation, needle biopsy, e.g., transthoracic needle aspiration, cervical mediastinoscopy, endoscopic

lymph node biopsy, video-assisted thoracoscopy, exploratory thoracotomy, bone marrow biopsy and bone marrow aspiration.

All the methods of the present invention may optionally include determining the expression levels of one or more other cancer markers in addition to determining the expression level of a BSNA or BSP. In many cases, the use of another cancer marker will decrease the likelihood of false positives or false negatives. In one embodiment, the one or more other cancer markers include other BSNA or BSPs as disclosed herein. Other cancer markers useful in the present invention will depend on the cancer being tested and are known to those of skill in the art. In a preferred embodiment, at least one other cancer marker in addition to a particular BSNA or BSP is measured. In a more preferred embodiment, at least two other additional cancer markers are used. In an even more preferred embodiment, at least three, more preferably at least five, even more preferably at least ten additional cancer markers are used.

Diagnosing

In one aspect, the invention provides a method for determining the expression levels and/or structural alterations of one or more BSNA and/or BSP in a sample from a patient suspected of having breast cancer. In general, the method comprises the steps of obtaining the sample from the patient, determining the expression level or structural alterations of a BSNA and/or BSP and then ascertaining whether the patient has breast cancer from the expression level of the BSNA or BSP. In general, if high expression relative to a control of a BSNA or BSP is indicative of breast cancer, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least one and a half times higher, and more preferably are at least two times higher, still more preferably five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of breast cancer, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least one and a half times lower, and more preferably are at least two times lower, still more preferably five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

The present invention also provides a method of determining whether breast cancer has metastasized in a patient. One may identify whether the breast cancer has metastasized by measuring the expression levels and/or structural alterations of one or more BSNA and/or BSPs in a variety of tissues. The presence of a BSNA or BSP in a tissue other than breast at levels higher than that of corresponding noncancerous tissue (e.g., the same tissue from another individual) is indicative of metastasis if high level expression of a BSNA or BSP is associated with breast cancer. Similarly, the presence of a BSNA or BSP in a tissue other than breast at levels lower than that of corresponding noncancerous tissue is indicative of metastasis if low level expression of a BSNA or BSP is associated with breast cancer. Further, the presence of a structurally altered BSNA or BSP that is associated with breast cancer is also indicative of metastasis.

In general, if high expression relative to a control of a BSNA or BSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of the BSNA or BSP is at least one and a half times higher, and more preferably are at least two times higher, still more preferably five times higher, even more preferably at least ten times higher, than in preferably the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of metastasis, an assay for metastasis is considered positive if the level of expression of the BSNA or BSP is at least one and a half times lower, and more preferably are at least two times lower, still more preferably five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid of a normal human control.

Staging

The invention also provides a method of staging breast cancer in a human patient.

25 The method comprises identifying a human patient having breast cancer and analyzing cells, tissues or bodily fluids from such human patient for expression levels and/or structural alterations of one or more BSNA and/or BSPs. First, one or more tumors from a variety of patients are staged according to procedures well known in the art, and the expression levels of one or more BSNA and/or BSPs is determined for each stage to obtain a standard expression level for each BSNA and/or BSP. Then, the BSNA and/or BSP expression levels of the BSNA and/or BSP are determined in a biological sample from a patient whose stage of cancer is not known. The BSNA and/or BSP expression levels from the patient are

then compared to the standard expression level. By comparing the expression level of the BSNA^s and BSP^s from the patient to the standard expression levels, one may determine the stage of the tumor. The same procedure may be followed using structural alterations of a BSNA or BSP to determine the stage of a breast cancer.

5 *Monitoring*

Further provided is a method of monitoring breast cancer in a human patient. One may monitor a human patient to determine whether there has been metastasis and, if there has been, when metastasis began to occur. One may also monitor a human patient to determine whether a preneoplastic lesion has become cancerous. One may also monitor a 10 human patient to determine whether a therapy, e.g., chemotherapy, radiotherapy or surgery, has decreased or eliminated the breast cancer. The monitoring may determine if there has been a reoccurrence and, if so, determine its nature. The method comprises identifying a human patient that one wants to monitor for breast cancer, periodically analyzing cells, tissues or bodily fluids from such human patient for expression levels of 15 one or more BSNA^s or BSP^s, and comparing the BSNA or BSP levels over time to those BSNA or BSP expression levels obtained previously. Patients may also be monitored by measuring one or more structural alterations in a BSNA or BSP that are associated with breast cancer.

If increased expression of a BSNA or BSP is associated with metastasis, treatment 20 failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting an increase in the expression level of a BSNA or BSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. One having ordinary skill in the art would recognize that if this were the case, then a decreased expression level would be indicative of no metastasis, effective therapy or failure to 25 progress to a neoplastic lesion. If decreased expression of a BSNA or BSP is associated with metastasis, treatment failure, or conversion of a preneoplastic lesion to a cancerous lesion, then detecting a decrease in the expression level of a BSNA or BSP indicates that the tumor is metastasizing, that treatment has failed or that the lesion is cancerous, respectively. In a preferred embodiment, the levels of BSNA^s or BSP^s are determined 30 from the same cell type, tissue or bodily fluid as prior patient samples. Monitoring a patient for onset of breast cancer metastasis is periodic and preferably is done on a quarterly basis, but may be done more or less frequently.

The methods described herein can further be utilized as prognostic assays to identify subjects having or at risk of developing a disease or disorder associated with increased or decreased expression levels of a BSNA and/or BSP. The present invention provides a method in which a test sample is obtained from a human patient and one or 5 more BSNA and/or BSPs are detected. The presence of higher (or lower) BSNA or BSP levels as compared to normal human controls is diagnostic for the human patient being at risk for developing cancer, particularly breast cancer. The effectiveness of therapeutic agents to decrease (or increase) expression or activity of one or more BSNA and/or BSPs of the invention can also be monitored by analyzing levels of expression of the BSNA and/or BSPs in a human patient in clinical trials or in *in vitro* screening assays such as in 10 human cells. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the human patient or cells, as the case may be, to the agent being tested.

Detection of Genetic Lesions or Mutations

15 The methods of the present invention can also be used to detect genetic lesions or mutations in a BSG, thereby determining if a human with the genetic lesion is susceptible to developing breast cancer or to determine what genetic lesions are responsible, or are partly responsible, for a person's existing breast cancer. Genetic lesions can be detected, for example, by ascertaining the existence of a deletion, insertion and/or substitution of 20 one or more nucleotides from the BSGs of this invention, a chromosomal rearrangement of a BSG, an aberrant modification of a BSG (such as of the methylation pattern of the genomic DNA), or allelic loss of a BSG. Methods to detect such lesions in the BSG of this invention are known to those having ordinary skill in the art following the teachings of the specification.

25 Methods of Detecting Noncancerous Breast Diseases

The present invention also provides methods for determining the expression levels and/or structural alterations of one or more BSNA and/or BSPs in a sample from a patient suspected of having or known to have a noncancerous breast disease. In general, the method comprises the steps of obtaining a sample from the patient, determining the 30 expression level or structural alterations of a BSNA and/or BSP, comparing the expression level or structural alteration of the BSNA or BSP to a normal breast control, and then ascertaining whether the patient has a noncancerous breast disease. In general, if high

expression relative to a control of a BSNA or BSP is indicative of a particular noncancerous breast disease, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least two times higher, and more preferably are at least five times higher, even more preferably at least ten times higher, than in preferably 5 the same cells, tissues or bodily fluid of a normal human control. In contrast, if low expression relative to a control of a BSNA or BSP is indicative of a noncancerous breast disease, a diagnostic assay is considered positive if the level of expression of the BSNA or BSP is at least two times lower, more preferably are at least five times lower, even more preferably at least ten times lower than in preferably the same cells, tissues or bodily fluid 10 of a normal human control. The normal human control may be from a different patient or from uninvolved tissue of the same patient.

One having ordinary skill in the art may determine whether a BSNA and/or BSP is associated with a particular noncancerous breast disease by obtaining breast tissue from a patient having a noncancerous breast disease of interest and determining which BSNA 15 and/or BSPs are expressed in the tissue at either a higher or a lower level than in normal breast tissue. In another embodiment, one may determine whether a BSNA or BSP exhibits structural alterations in a particular noncancerous breast disease state by obtaining breast tissue from a patient having a noncancerous breast disease of interest and determining the structural alterations in one or more BSNA and/or BSPs relative to 20 normal breast tissue.

Methods for Identifying Breast Tissue

In another aspect, the invention provides methods for identifying breast tissue. These methods are particularly useful in, *e.g.*, forensic science, breast cell differentiation and development, and in tissue engineering.

25 In one embodiment, the invention provides a method for determining whether a sample is breast tissue or has breast tissue-like characteristics. The method comprises the steps of providing a sample suspected of comprising breast tissue or having breast tissue-like characteristics, determining whether the sample expresses one or more BSNA and/or BSPs, and, if the sample expresses one or more BSNA and/or BSPs, concluding that the 30 sample comprises breast tissue. In a preferred embodiment, the BSNA encodes a polypeptide having an amino acid sequence selected from SEQ ID NO: 73-179, or a homolog, allelic variant or fragment thereof. In a more preferred embodiment, the BSNA

has a nucleotide sequence selected from SEQ ID NO: 1-72, or a hybridizing nucleic acid, an allelic variant or a part thereof. Determining whether a sample expresses a BSNA can be accomplished by any method known in the art. Preferred methods include hybridization to microarrays, Northern blot hybridization, and quantitative or qualitative 5 RT-PCR. In another preferred embodiment, the method can be practiced by determining whether a BSP is expressed. Determining whether a sample expresses a BSP can be accomplished by any method known in the art. Preferred methods include Western blot, ELISA, RIA and 2D PAGE. In one embodiment, the BSP has an amino acid sequence selected from SEQ ID NO: 73-179, or a homolog, allelic variant or fragment thereof. In 10 another preferred embodiment, the expression of at least two BSNAs and/or BSPs is determined. In a more preferred embodiment, the expression of at least three, more preferably four and even more preferably five BSNAs and/or BSPs are determined.

In one embodiment, the method can be used to determine whether an unknown tissue is breast tissue. This is particularly useful in forensic science, in which small, 15 damaged pieces of tissues that are not identifiable by microscopic or other means are recovered from a crime or accident scene. In another embodiment, the method can be used to determine whether a tissue is differentiating or developing into breast tissue. This is important in monitoring the effects of the addition of various agents to cell or tissue culture, *e.g.*, in producing new breast tissue by tissue engineering. These agents include, 20 *e.g.*, growth and differentiation factors, extracellular matrix proteins and culture medium. Other factors that may be measured for effects on tissue development and differentiation include gene transfer into the cells or tissues, alterations in pH, aqueous:air interface and various other culture conditions.

Methods for Producing and Modifying Breast Tissue

25 In another aspect, the invention provides methods for producing engineered breast tissue or cells. In one embodiment, the method comprises the steps of providing cells, introducing a BSNA or a BSG into the cells, and growing the cells under conditions in which they exhibit one or more properties of breast tissue cells. In a preferred embodiment, the cells are pluripotent. As is well known in the art, normal breast tissue 30 comprises a large number of different cell types. Thus, in one embodiment, the engineered breast tissue or cells comprises one of these cell types. In another embodiment, the engineered breast tissue or cells comprises more than one breast cell

type. Further, the culture conditions of the cells or tissue may require manipulation in order to achieve full differentiation and development of the breast cell tissue. Methods for manipulating culture conditions are well known in the art.

- Nucleic acid molecules encoding one or more BSPs are introduced into cells,
5 preferably pleuripotent cells. In a preferred embodiment, the nucleic acid molecules encode BSPs having amino acid sequences selected from SEQ ID NO: 73-179, or homologous proteins, analogs, allelic variants or fragments thereof. In a more preferred embodiment, the nucleic acid molecules have a nucleotide sequence selected from SEQ ID NO: 1-72, or hybridizing nucleic acids, allelic variants or parts thereof. In another highly
10 preferred embodiment, a BSG is introduced into the cells. Expression vectors and methods of introducing nucleic acid molecules into cells are well known in the art and are described in detail, *supra*.

Artificial breast tissue may be used to treat patients who have lost some or all of their breast function.

15 **Pharmaceutical Compositions**

- In another aspect, the invention provides pharmaceutical compositions comprising the nucleic acid molecules, polypeptides, fusion proteins, antibodies, antibody derivatives, antibody fragments, agonists, antagonists, or inhibitors of the present invention. In a preferred embodiment, the pharmaceutical composition comprises a BSNA or part thereof.
20 In a more preferred embodiment, the BSNA has a nucleotide sequence selected from the group consisting of SEQ ID NO: 1-72, a nucleic acid that hybridizes thereto, an allelic variant thereof, or a nucleic acid that has substantial sequence identity thereto. In another preferred embodiment, the pharmaceutical composition comprises a BSP or fragment thereof. In a more preferred embodiment, the pharmaceutical composition comprises a
25 BSP having an amino acid sequence that is selected from the group consisting of SEQ ID NO: 73-179, a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof. In another preferred embodiment, the pharmaceutical composition comprises an anti-BSP antibody, preferably an antibody that specifically binds to a BSP having an amino acid that is selected from the
30 group consisting of SEQ ID NO: 73-179, or an antibody that binds to a polypeptide that is homologous thereto, a fusion protein comprising all or a portion of the polypeptide, or an analog or derivative thereof.

Due to the association of angiogenesis with cancer vascularization there is great need of new markers and methods for diagnosing angiogenesis activity to identify developing tumors and angiogenesis related diseases. Furthermore, great need is also present for new molecular targets useful in the treatment of angiogenesis and angiogenesis
5 related diseases such as cancer. In addition known modulators of angiogenesis such as endostatin or vascular endothelial growth factor (VEGF). Use of the methods and compositions disclosed herein in combination with anti-angiogenesis drugs, drugs that block the matrix breakdown (such as BMS-275291, Dalteparin (Fragmin®), Suramin), drugs that inhibit endothelial cells (2-methoxyestradiol (2-ME), CC-5013 (Thalidomide
10 Analog), Combretastatin A4 Phosphate, LY317615 (Protein Kinase C Beta Inhibitor), Soy Isoflavone (Genistein; Soy Protein Isolate), Thalidomide), drugs that block activators of angiogenesis (AE-941 (Neovastat™; GW786034), Anti-VEGF Antibody (Bevacizumab; Avastin™), Interferon-alpha, PTK787/ZK 222584, VEGF-Trap, ZD6474), Drugs that inhibit endothelial-specific integrin/survival signaling (EMD 121974, Anti-Anb3 Integrin
15 Antibody (Medi-522; Vitaxin™)).

Such a composition typically contains from about 0.1 to 90% by weight of a therapeutic agent of the invention formulated in and/or with a pharmaceutically acceptable carrier or excipient.

Pharmaceutical formulation is a well-established art that is further described in
20 Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th ed., Lippincott, Williams & Wilkins (2000); Ansel *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed., Lippincott Williams & Wilkins (1999); and Kibbe (ed.), Handbook of Pharmaceutical Excipients American Pharmaceutical Association, 3rd ed. (2000) and thus need not be described in detail herein.

Briefly, formulation of the pharmaceutical compositions of the present invention will depend upon the route chosen for administration. The pharmaceutical compositions utilized in this invention can be administered by various routes including both enteral and parenteral routes, including oral, intravenous, intramuscular, subcutaneous, inhalation, topical, sublingual, rectal, intra-arterial, intramedullary, intrathecal, intraventricular,
30 transmucosal, transdermal, intranasal, intraperitoneal, intrapulmonary, and intrauterine.

Oral dosage forms can be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Solid formulations of the compositions for oral administration can contain suitable carriers or excipients, such as carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or microcrystalline cellulose; gums including arabic and tragacanth; proteins such as gelatin and collagen; inorganics, such as kaolin, calcium carbonate, dicalcium phosphate, sodium chloride; and other agents such as acacia and alginic acid.

Agents that facilitate disintegration and/or solubilization can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate, microcrystalline cellulose, cornstarch, sodium starch glycolate, and alginic acid.

Tablet binders that can be used include acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (PovidoneTM), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

Lubricants that can be used include magnesium stearates, stearic acid, silicone fluid, talc, waxes, oils, and colloidal silica.

Fillers, agents that facilitate disintegration and/or solubilization, tablet binders and lubricants, including the aforementioned, can be used singly or in combination.

Solid oral dosage forms need not be uniform throughout. For example, dragee cores can be used in conjunction with suitable coatings, such as concentrated sugar solutions, which can also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

Oral dosage forms of the present invention include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Additionally, dyestuffs or pigments can be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, *i.e.*, dosage.

Liquid formulations of the pharmaceutical compositions for oral (enteral) administration are prepared in water or other aqueous vehicles and can contain various suspending agents such as methylcellulose, alginates, tragacanth, pectin, kelgin, carrageenan, acacia, polyvinylpyrrolidone, and polyvinyl alcohol. The liquid formulations 5 can also include solutions, emulsions, syrups and elixirs containing, together with the active compound(s), wetting agents, sweeteners, and coloring and flavoring agents.

The pharmaceutical compositions of the present invention can also be formulated for parenteral administration. Formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions.

10 For intravenous injection, water soluble versions of the compounds of the present invention are formulated in, or if provided as a lyophilate, mixed with, a physiologically acceptable fluid vehicle, such as 5% dextrose ("D5"), physiologically buffered saline, 0.9% saline, Hanks' solution, or Ringer's solution. Intravenous formulations may include carriers, excipients or stabilizers including, without limitation, calcium, human serum 15 albumin, citrate, acetate, calcium chloride, carbonate, and other salts.

Intramuscular preparations, *e.g.* a sterile formulation of a suitable soluble salt form of the compounds of the present invention, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution. Alternatively, a suitable insoluble form of the compound can be prepared and 20 administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, such as an ester of a long chain fatty acid (*e.g.*, ethyl oleate), fatty oils such as sesame oil, triglycerides, or liposomes.

25 Parenteral formulations of the compositions can contain various carriers such as vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like).

Aqueous injection suspensions can also contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Non-lipid polycationic amino polymers can also be used for delivery. Optionally, the 30 suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Pharmaceutical compositions of the present invention can also be formulated to permit injectable, long-term, deposition. Injectable depot forms may be made by forming

microencapsulated matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot 5 injectable formulations are also prepared by entrapping the drug in microemulsions that are compatible with body tissues.

The pharmaceutical compositions of the present invention can be administered topically. For topical use the compounds of the present invention can also be prepared in suitable forms to be applied to the skin, or mucus membranes of the nose and throat, and 10 can take the form of lotions, creams, ointments, liquid sprays or inhalants, drops, tinctures, lozenges, or throat paints. Such topical formulations further can include chemical compounds such as dimethylsulfoxide (DMSO) to facilitate surface penetration of the active ingredient. In other transdermal formulations, typically in patch-delivered 15 formulations, the pharmaceutically active compound is formulated with one or more skin penetrants, such as 2-N-methyl-pyrrolidone (NMP) or Azone. A topical semi-solid ointment formulation typically contains a concentration of the active ingredient from about 1 to 20%, *e.g.*, 5 to 10%, in a carrier such as a pharmaceutical cream base.

For application to the eyes or ears, the compounds of the present invention can be presented in liquid or semi-liquid form formulated in hydrophobic or hydrophilic bases as 20 ointments, creams, lotions, paints or powders.

For rectal administration the compounds of the present invention can be administered in the form of suppositories admixed with conventional carriers such as cocoa butter, wax or other glyceride.

Inhalation formulations can also readily be formulated. For inhalation, various 25 powder and liquid formulations can be prepared. For aerosol preparations, a sterile formulation of the compound or salt form of the compound may be used in inhalers, such as metered dose inhalers, and nebulizers. Aerosolized forms may be especially useful for treating respiratory disorders.

Alternatively, the compounds of the present invention can be in powder form for 30 reconstitution in the appropriate pharmaceutically acceptable carrier at the time of delivery.

The pharmaceutically active compound in the pharmaceutical compositions of the present invention can be provided as the salt of a variety of acids, including but not limited

to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

After pharmaceutical compositions have been prepared, they are packaged in an appropriate container and labeled for treatment of an indicated condition.

The active compound will be present in an amount effective to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

A "therapeutically effective dose" refers to that amount of active ingredient, for example BSP polypeptide, fusion protein, or fragments thereof, antibodies specific for BSP, agonists, antagonists or inhibitors of BSP, which ameliorates the signs or symptoms of the disease or prevent progression thereof; as would be understood in the medical arts, cure, although desired, is not required.

The therapeutically effective dose of the pharmaceutical agents of the present invention can be estimated initially by *in vitro* tests, such as cell culture assays, followed by assay in model animals, usually mice, rats, rabbits, dogs, or pigs. The animal model can also be used to determine an initial preferred concentration range and route of administration.

For example, the ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population) can be determined in one or more cell culture of animal model systems. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as LD50/ED50. Pharmaceutical compositions that exhibit large therapeutic indices are preferred.

The data obtained from cell culture assays and animal studies are used in formulating an initial dosage range for human use, and preferably provide a range of circulating concentrations that includes the ED50 with little or no toxicity. After administration, or between successive administrations, the circulating concentration of active agent varies within this range depending upon pharmacokinetic factors well known in the art, such as the dosage form employed, sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors specific to the subject requiring treatment. Factors that can be taken into account by the practitioner include the severity of the disease state, general health of the subject, age,

weight, gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

5 Normal dosage amounts may vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration. Where the therapeutic agent is a protein or antibody of the present invention, the therapeutic protein or antibody agent typically is administered at a daily dosage of 0.01 mg to 30 mg/kg of body weight of the patient (*e.g.*, 1mg/kg to 5 mg/kg). The pharmaceutical formulation can be
10 administered in multiple doses per day, if desired, to achieve the total desired daily dose.

Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells,
15 conditions, locations, etc.

Conventional methods, known to those of ordinary skill in the art of medicine, can be used to administer the pharmaceutical formulation(s) of the present invention to the patient. The pharmaceutical compositions of the present invention can be administered alone, or in combination with other therapeutic agents or interventions.

20 Therapeutic Methods

The present invention further provides methods of treating subjects having defects in a gene of the invention, *e.g.*, in expression, activity, distribution, localization, and/or solubility, which can manifest as a disorder of breast function. As used herein, "treating" includes all medically-acceptable types of therapeutic intervention, including palliation
25 and prophylaxis (prevention) of disease. The term "treating" encompasses any improvement of a disease, including minor improvements. These methods are discussed below.

Gene Therapy and Vaccines

The isolated nucleic acids of the present invention can also be used to drive *in vivo* expression of the polypeptides of the present invention. *In vivo* expression can be driven from a vector, typically a viral vector, often a vector based upon a replication incompetent retrovirus, an adenovirus, or an adeno-associated virus (AAV), for the purpose of gene

therapy. *In vivo* expression can also be driven from signals endogenous to the nucleic acid or from a vector, often a plasmid vector, such as pVAX1 (Invitrogen, Carlsbad, CA, USA), for purpose of “naked” nucleic acid vaccination, as further described in U.S. Patent Nos. 5,589,466; 5,679,647; 5,804,566; 5,830,877; 5,843,913; 5,880,104; 5,958,891; 5,985,847; 6,017,897; 6,110,898; 6,204,250, the disclosures of which are incorporated herein by reference in their entireties. For cancer therapy, it is preferred that the vector also be tumor-selective. *See, e.g.*, Doronin *et al.*, *J. Virol.* 75: 3314-24 (2001).

In another embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a nucleic acid molecule of the present invention is administered. The nucleic acid molecule can be delivered in a vector that drives expression of a BSP, fusion protein, or fragment thereof, or without such vector. Nucleic acid compositions that can drive expression of a BSP are administered, for example, to complement a deficiency in the native BSP, or as DNA vaccines. Expression vectors derived from virus, replication deficient retroviruses, adenovirus, adeno-associated (AAV) virus, herpes virus, or vaccinia virus can be used as can plasmids. *See, e.g.*, Cid-Arregui, *supra*. In a preferred embodiment, the nucleic acid molecule encodes a BSP having the amino acid sequence of SEQ ID NO: 73-179, or a fragment, fusion protein, allelic variant or homolog thereof.

In still other therapeutic methods of the present invention, pharmaceutical compositions comprising host cells that express a BSP, fusions, or fragments thereof can be administered. In such cases, the cells are typically autologous, so as to circumvent xenogeneic or allotypic rejection, and are administered to complement defects in BSP production or activity. In a preferred embodiment, the nucleic acid molecules in the cells encode a BSP having the amino acid sequence of SEQ ID NO: 73-179, or a fragment, fusion protein, allelic variant or homolog thereof.

Antisense Administration

Antisense nucleic acid compositions, or vectors that drive expression of a BSG antisense nucleic acid, are administered to downregulate transcription and/or translation of a BSG in circumstances in which excessive production, or production of aberrant protein, is the pathophysiologic basis of disease.

Antisense compositions useful in therapy can have a sequence that is complementary to coding or to noncoding regions of a BSG. For example,

oligonucleotides derived from the transcription initiation site, *e.g.*, between positions -10 and +10 from the start site, are preferred.

- Catalytic antisense compositions, such as ribozymes, that are capable of sequence-specific hybridization to BSG transcripts, are also useful in therapy. *See, e.g.,*
- 5 Phylactou, *Adv. Drug Deliv. Rev.* 44(2-3): 97-108 (2000); Phylactou *et al.*, *Hum. Mol. Genet.* 7(10): 1649-53 (1998); Rossi, *Ciba Found. Symp.* 209: 195-204 (1997); and Sigurdsson *et al.*, *Trends Biotechnol.* 13(8): 286-9 (1995).

Other nucleic acids useful in the therapeutic methods of the present invention are those that are capable of triplex helix formation in or near the BSG genomic locus. Such 10 triplexing oligonucleotides are able to inhibit transcription. *See, e.g.,* Intody *et al.*, *Nucleic Acids Res.* 28(21): 4283-90 (2000); and McGuffie *et al.*, *Cancer Res.* 60(14): 3790-9 (2000). Pharmaceutical compositions comprising such triplex forming oligos (TFOs) are administered in circumstances in which excessive production, or production of aberrant protein, is a pathophysiologic basis of disease.

15 In a preferred embodiment, the antisense molecule is derived from a nucleic acid molecule encoding a BSP, preferably a BSP comprising an amino acid sequence of SEQ ID NO: 73-179, or a fragment, allelic variant or homolog thereof. In a more preferred embodiment, the antisense molecule is derived from a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-72, or a part, allelic variant, substantially similar or 20 hybridizing nucleic acid thereof.

Polypeptide Administration

In one embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising a BSP, a fusion protein, fragment, analog or derivative thereof is administered to a subject with a 25 clinically-significant BSP defect.

Protein compositions are administered, for example, to complement a deficiency in native BSP. In other embodiments, protein compositions are administered as a vaccine to elicit a humoral and/or cellular immune response to BSP. The immune response can be used to modulate activity of BSP or, depending on the immunogen, to immunize against 30 aberrant or aberrantly expressed forms, such as mutant or inappropriately expressed isoforms. In yet other embodiments, protein fusions having a toxic moiety are administered to ablate cells that aberrantly accumulate BSP.

In a preferred embodiment, the polypeptide administered is a BSP comprising an amino acid sequence of SEQ ID NO: 73-179, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the polypeptide is encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-72, or a part, 5 allelic variant, substantially similar or hybridizing nucleic acid thereof.

Antibody, Agonist and Antagonist Administration

In another embodiment of the therapeutic methods of the present invention, a therapeutically effective amount of a pharmaceutical composition comprising an antibody (including fragment or derivative thereof) of the present invention is administered. As is 10 well known, antibody compositions are administered, for example, to antagonize activity of BSP, or to target therapeutic agents to sites of BSP presence and/or accumulation. In a preferred embodiment, the antibody specifically binds to a BSP comprising an amino acid sequence of SEQ ID NO: 73-179, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the antibody specifically binds to a 15 BSP encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-72, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

The present invention also provides methods for identifying modulators which bind to a BSP or have a modulatory effect on the expression or activity of a BSP.

Modulators which decrease the expression or activity of BSP (antagonists) are believed to 20 be useful in treating breast cancer. Such screening assays are known to those of skill in the art and include, without limitation, cell-based assays and cell-free assays. Small molecules predicted via computer imaging to specifically bind to regions of a BSP can also be designed, synthesized and tested for use in the imaging and treatment of breast cancer. Further, libraries of molecules can be screened for potential anticancer agents by 25 assessing the ability of the molecule to bind to the BSPs identified herein. Molecules identified in the library as being capable of binding to a BSP are key candidates for further evaluation for use in the treatment of breast cancer. In a preferred embodiment, these molecules will downregulate expression and/or activity of a BSP in cells.

In another embodiment of the therapeutic methods of the present invention, a 30 pharmaceutical composition comprising a non-antibody antagonist of BSP is administered. Antagonists of BSP can be produced using methods generally known in the art. In particular, purified BSP can be used to screen libraries of pharmaceutical agents, often

combinatorial libraries of small molecules, to identify those that specifically bind and antagonize at least one activity of a BSP.

In other embodiments a pharmaceutical composition comprising an agonist of a BSP is administered. Agonists can be identified using methods analogous to those used to 5 identify antagonists.

In a preferred embodiment, the antagonist or agonist specifically binds to and antagonizes or agonizes, respectively, a BSP comprising an amino acid sequence of SEQ ID NO: 73-179, or a fusion protein, allelic variant, homolog, analog or derivative thereof. In a more preferred embodiment, the antagonist or agonist specifically binds to and 10 antagonizes or agonizes, respectively, a BSP encoded by a nucleic acid molecule having a nucleotide sequence of SEQ ID NO: 1-72, or a part, allelic variant, substantially similar or hybridizing nucleic acid thereof.

Targeting Breast Tissue

15 The invention also provides a method in which a polypeptide of the invention, or an antibody thereto, is linked to a therapeutic agent such that it can be delivered to the breast or to specific cells in the breast. In a preferred embodiment, an anti-BSP antibody is linked to a therapeutic agent and is administered to a patient in need of such therapeutic agent. The therapeutic agent may be a toxin, if breast tissue needs to be selectively 20 destroyed. This would be useful for targeting and killing breast cancer cells. In another embodiment, the therapeutic agent may be a growth or differentiation factor, which would be useful for promoting breast cell function.

In another embodiment, an anti-BSP antibody may be linked to an imaging agent that can be detected using, e.g., magnetic resonance imaging, CT or PET. This would be 25 useful for determining and monitoring breast function, identifying breast cancer tumors, and identifying noncancerous breast diseases.

EXAMPLES

Example 1a: Alternative Splice Variants

We identified gene transcripts using the Gencarta™ tools (Compugen Ltd., Tel 30 Aviv, Israel) and a variety of public and proprietary databases. These splice variants are either sequences which differ from a previously defined sequence or new uses of known sequences. In general related variants are annotated as DEX0451_XXX.nt.1,

DEX0451_XXX.nt.2, DEX0451_XXX.nt.3, etc. The variant DNA sequences encode proteins which differ from a previously defined protein sequence. In relation to the nucleotide sequence naming convention, protein variants are annotated as

DEX0451_XXX.aa.1, DEX0451_XXX.aa.2, etc., wherein transcript DEX0451_XXX.nt.1

5 encodes protein DEX0451_XXX.aa.1. A single transcript may encode a protein from an alternate Open Reading Frame (ORF) which is designated DEX0451_XXX.orf.1.

Additionally, multiple transcripts may encode for a single protein. In this case, DEX0451_XXX.nt.1 and DEX0451_XXX.nt.2 will both be associated with DEX0451_XXX.aa.1.

10 The mapping of the nucleic acid ("NT") SEQ ID NO; DEX ID; chromosomal location (if known); open reading frame (ORF) location; amino acid ("AA") SEQ ID NO; AA DEX ID; are shown in the table below.

SEQ ID NO	DEX ID	Chromo Map	ORF Loc	SEQ ID NO	DEX ID
1	DEX0451_001.nt.1	7q32.2	338-609	73	DEX0451_001.aa.1
1	DEX0451_001.nt.1	7q32.2	219-569	74	DEX0451_001.orf.1
2	DEX0451_001.nt.2	7q32.2	444-913	75	DEX0451_001.aa.2
2	DEX0451_001.nt.2	7q32.2	415-873	76	DEX0451_001.orf.2
3	DEX0451_002.nt.1	19p13.12	255-473	77	DEX0451_002.aa.1
4	DEX0451_003.nt.1	17q12	1-602	78	DEX0451_003.aa.1
5	DEX0451_004.nt.1	17q24.3	1-399	79	DEX0451_004.aa.1
5	DEX0451_004.nt.1	17q24.3	417-614	80	DEX0451_004.orf.1
6	DEX0451_005.nt.1	15	96-620	81	DEX0451_005.aa.1
7	DEX0451_006.nt.1	8q22.2	19-255	82	DEX0451_006.aa.1
8	DEX0451_006.nt.2	8q22.2	4-267	83	DEX0451_006.aa.2
9	DEX0451_006.nt.3	8q22.2	5-283	84	DEX0451_006.aa.3
10	DEX0451_006.nt.4	8q22.2	10-249	85	DEX0451_006.aa.4
11	DEX0451_006.nt.5	8q22.2	21-224	86	DEX0451_006.aa.5
12	DEX0451_006.nt.6	8q22.2	67-225	87	DEX0451_006.aa.6
13	DEX0451_006.nt.7	8q22.2	29-244	88	DEX0451_006.orf.7
13	DEX0451_006.nt.7	8q22.2	6-249	89	DEX0451_006.aa.7
14	DEX0451_006.nt.8	8q22.2	442-963	90	DEX0451_006.orf.8
14	DEX0451_006.nt.8	8q22.2	10-315	91	DEX0451_006.aa.8
15	DEX0451_007.nt.1	8q13.1	188-839	92	DEX0451_007.aa.1
15	DEX0451_007.nt.1	8q13.1	221-1276	93	DEX0451_007.orf.1
16	DEX0451_007.nt.2	8q13.1	574-793	94	DEX0451_007.aa.2
16	DEX0451_007.nt.2	8q13.1	905-1780	95	DEX0451_007.orf.2
17	DEX0451_007.nt.3	8q13.1	188-665	96	DEX0451_007.aa.3
17	DEX0451_007.nt.3	8q13.1	221-1105	97	DEX0451_007.orf.3
18	DEX0451_007.nt.4	8q13.1	710-1169	98	DEX0451_007.aa.4
18	DEX0451_007.nt.4	8q13.1	530-1162	99	DEX0451_007.orf.4

19	DEX0451_007.nt.5	8q13.1	1-447	100	DEX0451_007.aa.5
20	DEX0451_008.nt.1	1p34.1	63-659	101	DEX0451_008.aa.1
21	DEX0451_009.nt.1	17q12	1-152	102	DEX0451_009.aa.1
21	DEX0451_009.nt.1	17q12	3525-3920	103	DEX0451_009.orf.1
22	DEX0451_010.nt.1	2q35	5-217	104	DEX0451_010.aa.1
23	DEX0451_011.nt.1	12q13.11	179-709	105	DEX0451_011.aa.1
24	DEX0451_012.nt.1	20q13.33	150-678	106	DEX0451_012.aa.1
25	DEX0451_013.nt.1	6p12.3	707-2209	107	DEX0451_013.aa.1
26	DEX0451_013.nt.2	6p12.3	204-1581	108	DEX0451_013.aa.2
26	DEX0451_013.nt.2	6p12.3	172-1578	109	DEX0451_013.orf.2
27	DEX0451_014.nt.1	8p11.22	640-1242	110	DEX0451_014.aa.1
28	DEX0451_015.nt.1	10p12.1	388-790	111	DEX0451_015.aa.1
28	DEX0451_015.nt.1	10p12.1	1135-1605	112	DEX0451_015.orf.1
29	DEX0451_015.nt.2	10p12.1	389-751	113	DEX0451_015.aa.2
30	DEX0451_016.nt.1	12q13.13	824-1270	114	DEX0451_016.aa.1
30	DEX0451_016.nt.1	12q13.13	1568-2179	115	DEX0451_016.orf.1
31	DEX0451_016.nt.2	12q13.13	823-1273	114	DEX0451_016.aa.1
32	DEX0451_017.nt.1	17q12	74-655	116	DEX0451_017.aa.1
33	DEX0451_018.nt.1	X;53439399 -53447815	236-1651	117	DEX0451_018.aa.1
34	DEX0451_018.nt.2	X;53439399 -53447815	235-1822	118	DEX0451_018.aa.2
34	DEX0451_018.nt.2	X;53439399 -53447815	233-1174	119	DEX0451_018.orf.2
35	DEX0451_019.nt.1	17q12	1-108	120	DEX0451_019.aa.1
35	DEX0451_019.nt.1	17q12	652-891	121	DEX0451_019.orf.1
36	DEX0451_019.nt.2	17q12	1-102	122	DEX0451_019.aa.2
36	DEX0451_019.nt.2	17q12	633-872	123	DEX0451_019.orf.2
37	DEX0451_020.nt.1	18p11.22	178-400	124	DEX0451_020.aa.1
37	DEX0451_020.nt.1	18p11.22	3508-3789	125	DEX0451_020.orf.1
38	DEX0451_020.nt.2	18p11.22	1-165	126	DEX0451_020.aa.2
38	DEX0451_020.nt.2	18p11.22	3090-3371	127	DEX0451_020.orf.2
39	DEX0451_021.nt.1	10q26.2	139-990	128	DEX0451_021.aa.1
40	DEX0451_021.nt.2	10q26.2	139-798	129	DEX0451_021.aa.2
41	DEX0451_021.nt.3	10q26.2	139-708	130	DEX0451_021.aa.3
42	DEX0451_022.nt.1	8q21.11	263-1177	131	DEX0451_022.aa.1
43	DEX0451_023.nt.1	8q22.1	351-2100	132	DEX0451_023.aa.1
44	DEX0451_024.nt.1	X;75410607 -75423029	4-1170	133	DEX0451_024.aa.1
45	DEX0451_025.nt.1	1p36.11	176-538	134	DEX0451_025.aa.1
46	DEX0451_026.nt.1	7q22.1	13-376	135	DEX0451_026.aa.1
47	DEX0451_026.nt.2	7q22.1	121-816	136	DEX0451_026.aa.2
48	DEX0451_027.nt.1	14q12	1328-3077	137	DEX0451_027.aa.1
48	DEX0451_027.nt.1	14q12	1314-2681	138	DEX0451_027.orf.1
49	DEX0451_028.nt.1	22q13.31	990-2064	139	DEX0451_028.aa.1
49	DEX0451_028.nt.1	22q13.31	1049-2059	140	DEX0451_028.orf.1
50	DEX0451_028.nt.2	22q13.31	50-764	141	DEX0451_028.aa.2
50	DEX0451_028.nt.2	22q13.31	18-761	142	DEX0451_028.orf.2

51	DEX0451_029.nt.1	4q31.1	24-362	143	DEX0451_029.aa.1
52	DEX0451_030.nt.1	2q33.1	480-726	144	DEX0451_030.aa.1
52	DEX0451_030.nt.1	2q33.1	40-417	145	DEX0451_030.orf.1
53	DEX0451_030.nt.2	2q33.1	913-1290	146	DEX0451_030.aa.2
54	DEX0451_031.nt.1	6p21.33	142-630	147	DEX0451_031.aa.1
54	DEX0451_031.nt.1	6p21.33	26-628	148	DEX0451_031.orf.1
55	DEX0451_032.nt.1	17q12	136-644	149	DEX0451_032.aa.1
55	DEX0451_032.nt.1	17q12	3-584	150	DEX0451_032.orf.1
56	DEX0451_032.nt.2	17q12	155-949	151	DEX0451_032.aa.2
57	DEX0451_032.nt.3	17q12	1-210	152	DEX0451_032.aa.3
57	DEX0451_032.nt.3	17q12	21-257	153	DEX0451_032.orf.3
58	DEX0451_032.nt.4	17q12	1-172	154	DEX0451_032.aa.4
58	DEX0451_032.nt.4	17q12	2-271	155	DEX0451_032.orf.4
59	DEX0451_032.nt.5	17q12	88-1028	156	DEX0451_032.aa.5
59	DEX0451_032.nt.5	17q12	14-1027	157	DEX0451_032.orf.5
60	DEX0451_032.nt.6	17q12	518-1319	158	DEX0451_032.aa.6
60	DEX0451_032.nt.6	17q12	471-1259	159	DEX0451_032.orf.6
61	DEX0451_033.nt.1	15q21.1	163-483	160	DEX0451_033.aa.1
62	DEX0451_033.nt.2	15q21.1	16-142	161	DEX0451_033.aa.2
62	DEX0451_033.nt.2	15q21.1	143-283	162	DEX0451_033.orf.2
63	DEX0451_034.nt.1	19q13.32	491-1265	163	DEX0451_034.aa.1
64	DEX0451_035.nt.1	2p13.1	58-933	164	DEX0451_035.aa.1
64	DEX0451_035.nt.1	2p13.1	2-922	165	DEX0451_035.orf.1
65	DEX0451_036.nt.1	8q21.13	203-823	166	DEX0451_036.aa.1
66	DEX0451_036.nt.2	8q21.13	1-247	167	DEX0451_036.aa.2
66	DEX0451_036.nt.2	8q21.13	278-739	168	DEX0451_036.orf.2
67	DEX0451_036.nt.3	8q21.13	2-535	169	DEX0451_036.aa.3
68	DEX0451_037.nt.1	11q13.4	151-564	170	DEX0451_037.aa.1
68	DEX0451_037.nt.1	11q13.4	2-562	171	DEX0451_037.orf.1
69	DEX0451_037.nt.2	11q13.4	289-895	172	DEX0451_037.aa.2
69	DEX0451_037.nt.2	11q13.4	2-1162	173	DEX0451_037.orf.2
70	DEX0451_037.nt.3	11q13.4	150-825	174	DEX0451_037.aa.3
70	DEX0451_037.nt.3	11q13.4	151-1092	175	DEX0451_037.orf.3
71	DEX0451_037.nt.4	11q13.4	908-1932	176	DEX0451_037.aa.4
71	DEX0451_037.nt.4	11q13.4	729-1664	177	DEX0451_037.orf.4
72	DEX0451_037.nt.5	11q13.4	71-569	178	DEX0451_037.aa.5
72	DEX0451_037.nt.5	11q13.4	101-565	179	DEX0451_037.orf.5

The polypeptides of the present invention were analyzed and the following attributes were identified; specifically, epitopes, post translational modifications, signal peptides and transmembrane domains. Antigenicity (Epitope) prediction was performed through the antigenic module in the EMBOSS package. Rice, P., EMBOSS: The European Molecular Biology Open Software Suite, *Trends in Genetics* 16(6): 276-277 (2000). The antigenic module predicts potentially antigenic regions of a protein sequence, using the method of Kolaskar and Tongaonkar. Kolaskar, AS and Tongaonkar, PC., A

semi-empirical method for prediction of antigenic determinants on protein antigens, *FEBS Letters* 276: 172-174 (1990). Examples of post-translational modifications (PTMs) and other motifs of the BSPs of this invention are listed below. In addition, antibodies that specifically bind such post-translational modifications may be useful as a diagnostic or as therapeutic.

The PTMs and other motifs were predicted by using the ProSite Dictionary of Proteins Sites and Patterns (Bairoch *et al.*, *Nucleic Acids Res.* 25(1):217-221 (1997)), the following motifs, including PTMs, were predicted for the BSPs of the invention. The signal peptides were detected by using the SignalP 2.0, *see* Nielsen *et al.*, *Protein Engineering* 12, 3-9 (1999). Prediction of transmembrane helices in proteins was performed by the application TMHMM 2.0, "currently the best performing transmembrane prediction program", according to authors (Krogh *et al.*, *Journal of Molecular Biology*, 305(3):567-580, (2001); Moller *et al.*, *Bioinformatics*, 17(7):646-653, (2001); Sonnhammer, *et al.*, *A hidden Markov model for predicting transmembrane helices in protein sequences* in Glasgow, *et al.* Ed. Proceedings of the Sixth International Conference on Intelligent Systems for Molecular Biology, pages 175-182, Menlo Park, CA, 1998. AAAI Press. The PSORT II program may also be used to predict cellular localizations. Horton *et al.*, *Intelligent Systems for Molecular Biology* 5: 147-152 (1997). The table below includes the following sequence annotations: Signal peptide presence; TM (number of membrane domain, topology in orientation and position); Amino acid location and antigenic index (location, AI score); PTM and other motifs (type, amino acid residue locations); and functional domains (type, amino acid residue locations).

DEX ID	Sig P	TMHMM	Antigenicity	PTM	Domains
DEX0451_001.aa.1	N	0 - o1- 91;	49-55, 1.065; 61-72, 1.291;	PKC_PHOSPHO_SITE 8-10; MYRISTYL 74-79; CK2_PHOSPHO_SITE 6-9; MYRISTYL 45-50; CAMP_PHOSPHO_SITE 80-83; CAMP_PHOSPHO_SITE 27-30;	
DEX0451_001.orf.1	N	0 - o1- 117;	101- 112, 1.291; 6-12, 1.037; 89-95, 1.065; 24-48, 1.15;	PKC_PHOSPHO_SITE 48-50; MYRISTYL 85-90; CAMP_PHOSPHO_SITE 67-70; CK2_PHOSPHO_SITE 46-49;	
DEX0451_001.aa.2	N	0 - o1- 157;	115- 121, 1.065; 22-29, 1.069; 50-74, 1.15; 32-38, 1.037; 127- 138, 1.291;	CAMP_PHOSPHO_SITE 146- 149; MYRISTYL 140-145; MYRISTYL 111-116; PKC_PHOSPHO_SITE 3-5; CK2_PHOSPHO_SITE 72-75; PKC_PHOSPHO_SITE 74-76; CAMP_PHOSPHO_SITE 93-96;	

			8-14, 1.029;		
DEX0451_001.orf.	N	0 - o1- 153;	125- 131, 1.065; 60-84, 1.15; 42-48, 1.037; 18-24, 1.029; 137- 148, 1.291; 32-39, 1.069;	PKC_PHOSPHO_SITE 84-86; CAMP_PHOSPHO_SITE 103-106; PKC_PHOSPHO_SITE 13-15; MYRISTYL 121-126; CK2_PHOSPHO_SITE 82-85;	
DEX0451_002.aa.1	N	0 - o1- 73;	50-58, 1.118; 4-12, 1.151; 62-70, 1.098; 27-44, 1.213; 14-20, 1.074;	MYRISTYL 19-24; PKC_PHOSPHO_SITE 6-8; MYRISTYL 15-20; MYRISTYL 2-7;	
DEX0451_003.aa.1	N	0 - o1- 199;	123- 143, 1.128; 164- 171, 1.07; 112- 121, 1.149; 15-21, 1.074; 150- 156, 1.101; 95- 110, 1.163; 72-78, 1.104; 39-46, 1.1;	PKC_PHOSPHO_SITE 54-56; MYRISTYL 53-58; PKC_PHOSPHO_SITE 60-62; CK2_PHOSPHO_SITE 179-182; MYRISTYL 160-165; MYRISTYL 175-180; PKC_PHOSPHO_SITE 33-35; CAMP_PHOSPHO_SITE 111-114; MYRISTYL 26-31; AMIDATION 29-32; ASN_GLYCOSYLATION 188-191; PKC_PHOSPHO_SITE 179-181;	
DEX0451_004.aa.1	N	0 - o1- 132;	29-36, 1.087; 77-98, 1.184; 39-52, 1.073; 122- 129, 1.163; 8-15, 1.118;	ASN_GLYCOSYLATION 88-91; PKC_PHOSPHO_SITE 73-75; CK2_PHOSPHO_SITE 62-65; PKC_PHOSPHO_SITE 96-98; PKC_PHOSPHO_SITE 106-108; CK2_PHOSPHO_SITE 16-19; PKC_PHOSPHO_SITE 115-117; MYRISTYL 102-107; CK2_PHOSPHO_SITE 2-5; PKC_PHOSPHO_SITE 36-38;	
DEX0451_004.orf.	N	0 - o1- 66;	7-32, 1.133; 48-54, 1.11; 37-43, 1.074;	PKC_PHOSPHO_SITE 41-43; PKC_PHOSPHO_SITE 4-6; CK2_PHOSPHO_SITE 28-31; CK2_PHOSPHO_SITE 41-44; PKC_PHOSPHO_SITE 35-37; PKC_PHOSPHO_SITE 53-55; CK2_PHOSPHO_SITE 35-38;	
DEX0451_005.aa.1	N	0 - o1- 175;	100- 124, 1.141; 59-72, 1.121; 84-94, 1.153; 4-18, 1.091; 130- 172, 1.242; 26-36, 1.102;	PKC_PHOSPHO_SITE 126-128; MYRISTYL 82-87; CK2_PHOSPHO_SITE 50-53; ASN_GLYCOSYLATION 97-100; CK2_PHOSPHO_SITE 99-102; PKC_PHOSPHO_SITE 111-113; TYR_PHOSPHO_SITE 22-29;	LEURICH RPT 44-57; LRR 89-113; LRR cap 128-146; LEURICH RPT 87-100; LRR SDS22 50-120; LRR 65-88;
DEX0451_006.aa.1	N	1 - o1- 26:tm	16-21, 1.062; 4-12, 1.14; 26-48, 1.205;	MYRISTYL 73-78; PKC_PHOSPHO_SITE 77-79;	COX6C 5-79;

		27- 46; i4 7-79;			
DEX0451_006.aa.2	N	1 - o1- 34; tm 35- 52; i5 3-88;	25-30, 1.062; 7-21, 1.22; 35-57, 1.205;	PKC_PHOSPHO_SITE 86-88; MYRISTYL 82-87; MYRISTYL 9-14;	COX6C 14-88;
DEX0451_006.aa.3	N	1 - o1- 39; tm 40- 57; i5 8-93;	40-62, 1.205; 17-26, 1.087; 30-35, 1.062;	CK2_PHOSPHO_SITE 6-9; PKC_PHOSPHO_SITE 91-93; MYRISTYL 87-92;	COX6C 19-93;
DEX0451_006.aa.4	N	1 - o1- 27; tm 28- 47; i4 8-80;	17-22, 1.062; 7-13, 1.132; 27-49, 1.205;	PKC_PHOSPHO_SITE 78-80; MYRISTYL 74-79;	COX6C 6-80;
DEX0451_006.aa.5	Y	1 - o1- 14; tm 15- 32; i3 3-68;	15-37, 1.205; 5-10, 1.039;	MYRISTYL 62-67; PKC_PHOSPHO_SITE 66-68;	COX6C 1-68;
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DEX0451_007.aa.1	N	0 - o1- 216;	9-18,1.116; 124- 131,1.104; 192- 202,1.217; 48-54,1.105; 165- 185,1.078; 138- 149,1.061; 33-39,1.039; 76-99,1.149;	PKC_PHOSPHO_SITE 60-62; ASN_GLYCOSYLATION 5-8; ASN_GLYCOSYLATION 63-66; MYRISTYL 14-19; MYRISTYL 74-79; PKC_PHOSPHO_SITE 65-67; MYRISTYL 179-184; PKC_PHOSPHO_SITE 68-70; MYRISTYL 42-47; ASN_GLYCOSYLATION 59-62; PKC_PHOSPHO_SITE 213- 215; MYRISTYL 174-179; PKC_PHOSPHO_SITE 64-66; PKC_PHOSPHO_SITE 47-49; MYRISTYL 109-114; PKC_PHOSPHO_SITE 54-56; CK2_PHOSPHO_SITE 178- 181;	Mov34 80-194; JAB_MPN 84- 216; MPN_DOMAIN 83-173;
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DEX0451_ 019.orf. 2	Y	0 - o1- 80;	41-77,1.204; 7-37,1.162;	PKC_PHOSPHO_SITE 72-74; PKC_PHOSPHO_SITE 36-38; PKC_PHOSPHO_SITE 46-48; PKC_PHOSPHO_SITE 76-78;	
DEX0451_ 020.aa.1	N	0 - o1- 73;	5-14,1.193; 44-52,1.087; 54-60,1.096; 18-29,1.187;	MYRISTYL 68-73; MYRISTYL 15-20; MYRISTYL 63-68;	ATP_GTP_A 12- 19; RAB 6-73; RASTRNSFRMNG 47-69; RASTRNSFRMNG 6-27; RASTRNSFRMNG 29-45;
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		56;		PKC_PHOSPHO_SITE 35-37; TYR_PHOSPHO_SITE 28-36; ASN,GLYCOSYLATION 49-52; CK2_PHOSPHO_SITE 27-30;	
DEX0451_032.orf. 4	N	0 - i1- 90;	45-72,1.202; 21-37,1.139; 80-87,1.171;	MYRISTYL 18-23; MYRISTYL 28-33; MYRISTYL 68-73; PKC_PHOSPHO_SITE 7-9; MYRISTYL 61-66; PKC_PHOSPHO_SITE 41-43; MYRISTYL 40-45; AMIDATION 75-78;	
DEX0451_032_aa.5	N	0 - o1- 274- 315; 90- 101,1.095; 24-37,1.079; 126- 134,1.06; 230- 240,1.132; 209- 216,1.062;	149- 155,1.12; 66-75,1.074; 139- 144,1.047; 44-56,1.117; 186- 198,1.108; 294- 285,1.122; 101,1.095; 24-37,1.079; 126- 134,1.06; 230- 240,1.132; 209- 216,1.062;	CK2_PHOSPHO_SITE 167- 170; PKC_PHOSPHO_SITE 49-51; LEUCINE_ZIPPER 193-214; CK2_PHOSPHO_SITE 70-73; MYRISTYL 301-306; MYRISTYL 38-43; MYRISTYL 44-49; MYRISTYL 67-72; MYRISTYL 62-67; PKC_PHOSPHO_SITE 224- 226; CK2_PHOSPHO_SITE 254-257; MYRISTYL 59-64; MYRISTYL 16-21; MYRISTYL 230-235; MYRISTYL 227- 232; MYRISTYL 17-22; MYRISTYL 63-68; MYRISTYL 242-247; MYRISTYL 74-79; CK2_PHOSPHO_SITE 198- 201; PKC_PHOSPHO_SITE 22-24; PKC_PHOSPHO_SITE 272-274; CK2_PHOSPHO_SITE 93-96; PKC_PHOSPHO_SITE 5-7; CK2_PHOSPHO_SITE 133- 136; MYRISTYL 66-71; CAMP_PHOSPHO_SITE 299- 302; LEUCINE_ZIPPER 186- 207;	TYPE1KERATIN 158-171; TYPE1KERATIN 179-202; TYPE1KERATIN 233-253; filament 79- 313; GLY_RICH 16-78;
DEX0451_032.orf. 5	N	0 - o1- 338;		MYRISTYL 40-45; PKC_PHOSPHO_SITE 296- 298; LEUCINE_ZIPPER 210- 231; MYRISTYL 68-73; CK2_PHOSPHO_SITE 94-97; MYRISTYL 90-95; MYRISTYL 266-271; CK2_PHOSPHO_SITE 157- 160; PKC_PHOSPHO_SITE 73-75; MYRISTYL 62-67; CK2_PHOSPHO_SITE 117- 120; MYRISTYL 251-256; PKC_PHOSPHO_SITE 46-48; MYRISTYL 41-46; MYRISTYL 98-103; MYRISTYL 83-88; PKC_PHOSPHO_SITE 335- 337; CK2_PHOSPHO_SITE 222-225; PKC_PHOSPHO_SITE 29-31; MYRISTYL 254-259;	filament 103- 338; TYPE1KERATIN 203-226; TYPE1KERATIN 182-195; TYPE1KERATIN 257-277; GLY_RICH 40- 102;

				MYRISTYL 4-9; CK2_PHOSPHO_SITE 278- 281; PKC_PHOSPHO_SITE 329-331; PKC_PHOSPHO_SITE 248- 250; PKC_PHOSPHO_SITE 312-314; ASN_GLYCOSYLATION 6-9; MYRISTYL 323-328; MYRISTYL 91-96; MYRISTYL 86-91; LEUCINE_ZIPPER 217-238; MYRISTYL 87-92; PKC_PHOSPHO_SITE 309- 311; TYR_PHOSPHO_SITE 298-305; CK2_PHOSPHO_SITE 191- 194;	
DEX0451_032.aa.6	N	0 - 01- 266;	240- 247, 1.118; 148- 164, 1.078; 56-63, 1.062; 179- 199, 1.129; 4-11, 1.157; 256- 263, 1.123; 77-87, 1.132; 33-45, 1.108; 225- 235, 1.118;	CK2_PHOSPHO_SITE 120- 123; PKC_PHOSPHO_SITE 218-220; MYRISTYL 77-82; MYRISTYL 214-219; PKC_PHOSPHO_SITE 203- 205; CK2_PHOSPHO_SITE 170-173; LEUCINE_ZIPPER 40-61; CAMP_PHOSPHO_SITE 236-239; CK2_PHOSPHO_SITE 190- 193; LEUCINE_ZIPPER 33- 54; PKC_PHOSPHO_SITE 119-121; MYRISTYL 74-79; CK2_PHOSPHO_SITE 139- 142; PKC_PHOSPHO_SITE 71-73; MYRISTYL 253-258; CK2_PHOSPHO_SITE 45-48; PKC_PHOSPHO_SITE 162- 164; MYRISTYL 179-184; PKC_PHOSPHO_SITE 223- 225; CK2_PHOSPHO_SITE 101-104; MYRISTYL 89-94;	filament 2- 213; TYPE1KERATIN 178-204; TYPE1KERATIN 26-49; TYPE1KERATIN 80-100; TYPE1KERATIN 152-167;
DEX0451_032.orf.6	N	0 - 01- 263;	237- 248, 1.074; 49-61, 1.108; 19-27, 1.157; 195- 215, 1.129; 72-79, 1.062; 93- 103, 1.132; 164- 180, 1.078;	TYR_PHOSPHO_SITE 235- 243; PKC_PHOSPHO_SITE 242-244; CK2_PHOSPHO_SITE 245- 248; CK2_PHOSPHO_SITE 61-64; CK2_PHOSPHO_SITE 206-209; ASN_GLYCOSYLATION 256- 259; CK2_PHOSPHO_SITE 117-120; LEUCINE_ZIPPER 49-70; MYRISTYL 4-9; PKC_PHOSPHO_SITE 135- 137; CK2_PHOSPHO_SITE 234-237; PKC_PHOSPHO_SITE 87-89; PKC_PHOSPHO_SITE 219- 221; MYRISTYL 105-110; MYRISTYL 93-98; CK2_PHOSPHO_SITE 186- 189; LEUCINE_ZIPPER 56-	TYPE1KERATIN 96-116; TYPE1KERATIN 194-220; filament 5- 253; IF 240- 248; TYPE1KERATIN 168-183; TYPE1KERATIN 42-65;

				77; PKC_PHOSPHO_SITE 178-180; CK2_PHOSPHO_SITE 136- 139; MYRISTYL 90-95; MYRISTYL 195-200; CK2_PHOSPHO_SITE 155- 158;	
DEX0451_033.aa.1	Y	0 - o1- 107;	98- 104,1.088; 71-77,1.068; 26-33,1.102; 81-89,1.155; 4-21,1.216; 42-60,1.155;	CK2_PHOSPHO_SITE 91-94; PKC_PHOSPHO_SITE 24-26; CK2_PHOSPHO_SITE 53-56; CK2_PHOSPHO_SITE 103- 106; PKC_PHOSPHO_SITE 93-95; CK2_PHOSPHO_SITE 16-19; CK2_PHOSPHO_SITE 93-96;	IG_LIKE 25- 102; IGc1 40- 106;
DEX0451_033.aa.2	N	0 - i1- 41;	19-36,1.142;	CK2_PHOSPHO_SITE 15-18; PKC_PHOSPHO_SITE 15-17; CK2_PHOSPHO_SITE 13-16;	IG_MHC 20-26;
DEX0451_033.orf.2	Y	1 - o1- 14;tm 15- 34;i3 5-47;	10-44,1.246;	PKC_PHOSPHO_SITE 3-5;	
DEX0451_034.aa.1	N	0 - o1- 257;	10-17,1.098; 144- 152,1.168; 182- 208,1.135; 156- 168,1.253; 77-83,1.11; 91- 127,1.227; 39-58,1.144; 216- 245,1.17; 249- 254,1.087; 60-70,1.119; 25-34,1.124;	MYRISTYL 98-103; MYRISTYL 73-78; CK2_PHOSPHO_SITE 212- 215; MYRISTYL 141-146; CK2_PHOSPHO_SITE 2-5;	sp_Q15102_PA1 G_HUMAN 6- 246;
DEX0451_035.aa.1	Y	0 - o1- 292;	68-78,1.219; 242- 265,1.146; 193- 200,1.14; 271- 278,1.123; 206- 216,1.102; 127- 138,1.209; 5-52,1.146; 155- 178,1.122; 81-88,1.141; 227- 234,1.085;	MYRISTYL 223-228; CK2_PHOSPHO_SITE 107- 110; PKC_PHOSPHO_SITE 41-43; PKC_PHOSPHO_SITE 231-233; MICROBODIES_CTER 290- 292; AMIDATION 41-44; PKC_PHOSPHO_SITE 235- 237; CK2_PHOSPHO_SITE 109-112; PKC_PHOSPHO_SITE 22-24; MYRISTYL 206-211; ASN_GLYCOSYLATION 87-90; CK2_PHOSPHO_SITE 264- 267; CAMP_PHOSPHO_SITE 241-244; CK2_PHOSPHO SITE 235-	THFDHDRGNASE 189-209; THF_DHG_CYH 35-155; THF_DHG_CYH_C 157-285; sp_P13995_MTD C_HUMAN 49- 290; THFDHDRGNASE 144-165; THFDHDRGNASE 68-90; THFDHDRGNASE 109-136; THF_DHG_CYH_1 110-135;

			91-97, 1.141; 144- 151, 1.123; 282- 289, 1.128;	238;	
DEX0451_035.orf. 1	Y	0 ~ o1- 307;	146- 157, 1.209; 24-71, 1.146; 246- 253, 1.085; 261- 284, 1.146; 174- 197, 1.122; 225- 235, 1.102; 110- 116, 1.141; 6-16, 1.076; 87-97, 1.219; 212- 219, 1.14; 163- 170, 1.123; 100- 107, 1.141; 292- 297, 1.073;	MYRISTYL 225-230; CAMP_PHOSPHO_SITE 260- 263; PKC_PHOSPHO_SITE 250-252; CK2_PHOSPHO_SITE 128- 131; CK2_PHOSPHO_SITE 126-129; PKC_PHOSPHO_SITE 254- 256; CK2_PHOSPHO_SITE 254-257; PKC_PHOSPHO_SITE 41-43; AMIDATION 60-63; PKC_PHOSPHO_SITE 60-62; MYRISTYL 242-247; ASN_GLYCOSYLATION 106- 109;	THF_DHG_CYH_C 176-305; THF_DHG_CYH 54-174; THF_DHG_CYH_1 129-154; sp_P13995_MTD C_HUMAN 68- 293; THFDHDRGNASE 163-184; THFDHDRGNASE 128-155; THFDHDRGNASE 208-228; THFDHDRGNASE 87-109;
DEX0451_036.aa.1	N	0 ~ o1- 207;	89-95, 1.072; 109- 123, 1.118; 41-49, 1.032; 125- 147, 1.106; 8-13, 1.085; 182- 188, 1.057; 51-62, 1.148;	CK2_PHOSPHO_SITE 75-78; ASN_GLYCOSYLATION 190- 193; CK2_PHOSPHO_SITE 32-35; MYRISTYL 178-183; MYRISTYL 173-178; CAMP_PHOSPHO_SITE 97- 100; CK2_PHOSPHO_SITE 30-33; CK2_PHOSPHO_SITE 159-162; PKC_PHOSPHO_SITE 138- 140; MYRISTYL 107-112; PKC_PHOSPHO_SITE 156- 158; MYRISTYL 7-12; CK2_PHOSPHO_SITE 26-29; MYRISTYL 118-123; CK2_PHOSPHO_SITE 194- 197; PKC_PHOSPHO_SITE 122-124;	TPD52 4-194;
DEX0451_036.aa.2	N	0 ~ o1- 81;	8-19, 1.076; 50-59, 1.082; 32-44, 1.202; 65-71, 1.092;	MYRISTYL 61-66; MYRISTYL 55-60; MYRISTYL 74-79; AMIDATION 3-6; MYRISTYL 25-30;	
DEX0451_036.orf. 2	N	0 ~ o1- 154;	109- 123, 1.118; 51-62, 1.148; 41-49, 1.032; 89-95, 1.072; 4-13, 1.162;	MYRISTYL 107-112; CAMP_PHOSPHO_SITE 97- 100; MYRISTYL 7-12; CK2_PHOSPHO_SITE 32-35; PKC_PHOSPHO_SITE 122- 124; CK2_PHOSPHO_SITE 75-78; CK2_PHOSPHO_SITE 26-29; PKC_PHOSPHO_SITE	TPD52 7-149;

				133-135; MYRISTYL 118-123; CK2_PHOSPHO_SITE 30-33; CK2_PHOSPHO_SITE 136-139;	
DEX0451_036.aa.3	N	0 - o1- 178;	118- 135,1.148; 73-81,1.085; 18-27,1.06; 108- 116,1.032; 163- 175,1.203; 143- 149,1.046;	CK2_PHOSPHO_SITE 5-8; CK2_PHOSPHO_SITE 28-31; CAMP_PHOSPHO_SITE 37-40; PKC_PHOSPHO_SITE 161-163; MYRISTYL 25-30; CK2_PHOSPHO_SITE 99-102; PKC_PHOSPHO_SITE 61-63; CK2_PHOSPHO_SITE 97-100; MYRISTYL 74-79; CK2_PHOSPHO_SITE 93-96; MYRISTYL 54-59; PKC_PHOSPHO_SITE 40-42; CK2_PHOSPHO_SITE 32-35; CK2_PHOSPHO_SITE 142-145; PKC_PHOSPHO_SITE 28-30;	PRENYLATION 175-178; TPD52 71-176;
DEX0451_037.aa.1	N	0 - o1- 138;	71-89,1.15; 13-27,1.089; 47-59,1.162; 105- 135,1.091;	ASN_GLYCOSYLATION 44-47; PKC_PHOSPHO_SITE 133-135; CK2_PHOSPHO_SITE 35-38; PKC_PHOSPHO_SITE 32-34; CK2_PHOSPHO_SITE 81-84; PKC_PHOSPHO_SITE 118-120;	START 42-117; sp_Q9Y365_Q9Y 365_HUMAN 43-130;
DEX0451_037.orf.1	N	0 - o1- 187;		CK2_PHOSPHO_SITE 131-134; PKC_PHOSPHO_SITE 13-15; ASN_GLYCOSYLATION 94-97; CK2_PHOSPHO_SITE 26-29; PKC_PHOSPHO_SITE 82-84; CK2_PHOSPHO_SITE 85-88; CK2_PHOSPHO_SITE 173-176;	START 92-167; sp_Q9Y365_Q9Y 365_HUMAN 93-181;
DEX0451_037.aa.2	N	0 - o1- 201;	145- 156,1.091; 178- 189,1.183; 105- 124,1.09; 47-59,1.162; 13-27,1.089; 158- 175,1.16; 191- 198,1.099; 130- 136,1.067; 71-89,1.15;	PKC_PHOSPHO_SITE 118-120; ASN_GLYCOSYLATION 147-150; CK2_PHOSPHO_SITE 35-38; PKC_PHOSPHO_SITE 149-151; PKC_PHOSPHO_SITE 132-134; PKC_PHOSPHO_SITE 32-34; ASN_GLYCOSYLATION 44-47; CK2_PHOSPHO_SITE 81-84;	START 42-201; sp_Q9Y365_Q9Y 365_HUMAN 43-192;
DEX0451_037.orf.2	N	0 - o1- 387;	109- 123,1.089; 254- 271,1.16; 292- 306,1.131; 201- 220,1.09;	MYRISTYL 373-378; PKC_PHOSPHO_SITE 14-16; CK2_PHOSPHO_SITE 380-383; PKC_PHOSPHO_SITE 214-216; ASN_GLYCOSYLATION 243-246; MYRISTYL 376-381; CK2_PHOSPHO SITE 131-	ARG_RICH 23-90; sp_Q9Y365_Q9Y 365_HUMAN 139-318; START 117-322; START 117-322;

			143- 155, 1.162; 48-63, 1.091; 312- 319, 1.13; 226- 232, 1.067; 81-86, 1.051; 324- 354, 1.136; 274- 290, 1.19; 15-22, 1.056; 89-95, 1.11; 241- 252, 1.091; 167- 185, 1.15; 361- 366, 1.056;	134; PKC_PHOSPHO_SITE 245-247; ASN_GLYCOSYLATION 140- 143; CK2_PHOSPHO_SITE 367-370; PKC_PHOSPHO_SITE 228- 230; CK2_PHOSPHO_SITE 177-180; PKC_PHOSPHO_SITE 128- 130; ASN_GLYCOSYLATION 297-300;	START 138- 320;
DEX0451_037.aa.3	N	0 - o1- 224;	128- 147, 1.09; 168- 179, 1.091; 181- 198, 1.16; 36-50, 1.089; 70-82, 1.162; 16-22, 1.11; 153- 159, 1.067; 214- 221, 1.099; 94-112, 1.15; 201- 212, 1.183; 8-13, 1.051;	CK2_PHOSPHO_SITE 104- 107; PKC_PHOSPHO_SITE 55-57; CK2_PHOSPHO_SITE 58-61; ASN_GLYCOSYLATION 170-173; PKC_PHOSPHO_SITE 141- 143; PKC_PHOSPHO_SITE 172-174; ASN_GLYCOSYLATION 67-70; PKC_PHOSPHO_SITE 155- 157;	sp_Q9Y365_Q9Y 365_HUMAN 66- 215; START 65-224;
DEX0451_037.orf.3	N	0 - o1- 314;	288- 293, 1.056; 70-82, 1.162; 153- 159, 1.067; 239- 246, 1.13; 94-112, 1.15; 128- 147, 1.09; 251- 281, 1.136; 168- 179, 1.091; 219- 233, 1.131; 181- 198, 1.16; 36-50, 1.089; 8-13, 1.051; 201- 217, 1.19;	PKC_PHOSPHO_SITE 55-57; MYRISTYL 303-308; ASN_GLYCOSYLATION 224- 227; PKC_PHOSPHO_SITE 141-143; CK2_PHOSPHO_SITE 294- 297; MYRISTYL 300-305; CK2_PHOSPHO_SITE 307- 310; ASN_GLYCOSYLATION 67-70; PKC_PHOSPHO_SITE 172-174; CK2_PHOSPHO_SITE 58-61; CK2_PHOSPHO_SITE 104- 107; ASN_GLYCOSYLATION 170-173; PKC_PHOSPHO_SITE 155- 157;	START 44-249; START 44-249; sp_Q9Y365_Q9Y 365_HUMAN 66- 245; START 65-247;

			16-22, 1.11;		
DEX0451_037.aa.4	N	0 - o1- 341;	192- 227, 1.187; 258- 275, 1.115; 145- 156, 1.091; 326- 338, 1.221; 105- 124, 1.09; 178- 189, 1.183; 71-89, 1.15; 47-59, 1.162; 130- 136, 1.067; 242- 250, 1.163; 297- 307, 1.172; 13-27, 1.089; 158- 175, 1.16; 314- 320, 1.072;	PKC_PHOSPHO_SITE 290- 292; PKC_PHOSPHO_SITE 32-34; CK2_PHOSPHO_SITE 290-293; CK2_PHOSPHO_SITE 35-38; MYRISTYL 265-270; CK2_PHOSPHO_SITE 81-84; PKC_PHOSPHO_SITE 132- 134; MYRISTYL 273-278; ASN_GLYCOSYLATION 306- 309; CK2_PHOSPHO_SITE 294-297; PKC_PHOSPHO_SITE 284- 286; ASN_GLYCOSYLATION 44-47; CK2_PHOSPHO_SITE 248-251; ASN_GLYCOSYLATION 147- 150; PKC_PHOSPHO_SITE 149-151; CK2_PHOSPHO_SITE 308- 311; PKC_PHOSPHO_SITE 248-250; CK2_PHOSPHO_SITE 236- 239; PKC_PHOSPHO_SITE 118-120; MYRISTYL 189- 194;	ig 240-319; IG 232-335; IG_LIKE 224- 331; sp_Q9Y365_Q9Y 365_HUMAN 43- 210; START 42-201;
DEX0451_037.orf.4	N	0 - o1- 312;	190- 196, 1.067; 131- 149, 1.15; 205- 216, 1.091; 218- 235, 1.16; 10-39, 1.145; 165- 184, 1.09; 300- 308, 1.183; 73-87, 1.089; 238- 286, 1.245; 53-59, 1.094; 107- 119, 1.162;	PKC_PHOSPHO_SITE 92-94; ASN_GLYCOSYLATION 104- 107; CK2_PHOSPHO_SITE 36-39; PKC_PHOSPHO_SITE 192-194; PKC_PHOSPHO_SITE 209- 211; PKC_PHOSPHO_SITE 309-311; MYRISTYL 297- 302; MYRISTYL 278-283; PKC_PHOSPHO_SITE 178- 180; CK2_PHOSPHO_SITE 95-98; CK2_PHOSPHO_SITE 141-144; ASN_GLYCOSYLATION 207- 210;	sp_Q9Y365_Q9Y 365_HUMAN 103-261; START 102- 261; START 81-288;
DEX0451_037.aa.5	N	0 - o1- 165;	90-97, 1.13; 4-9, 1.079; 60-68, 1.054; 70-84, 1.131; 11-18, 1.057; 102- 132, 1.136; 139- 144, 1.056;	CK2_PHOSPHO_SITE 145- 148; MYRISTYL 154-159; ASN_GLYCOSYLATION 25-28; ASN_GLYCOSYLATION 75-78; ASN_GLYCOSYLATION 17-20; MYRISTYL 151-156; ASN_GLYCOSYLATION 41-44; CK2_PHOSPHO_SITE 158- 161; ASN_GLYCOSYLATION 33-36;	sp_Q9Y365_Q9Y 365_HUMAN 51- 96;
DEX0451_037.orf.	Y	0 - o1-	4-11, 1.132; 13-19, 1.03;	MYRISTYL 141-146; CK2_PHOSPHO SITE 148-	START 30-88; sp_Q9Y365_Q9Y

5		155;	21-27,1.03; 80-87,1.13; 29-35,1.03; 60-74,1.131; 42-58,1.19; 129- 134,1.056; 92- 122,1.136;	151; CK2_PHOSPHO_SITE 135-138; ASN GLYCOSYLATION 65-68; MYRISTYL 144-149;	365_HUMAN 42- 86;
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Example 1b: Sequence Alignment Support

Alignments between previously identified sequences and splice variant sequences are performed to confirm unique portions of splice variant nucleic acid and amino acid

5 sequences. The alignments are done using the Needle program in the European Molecular Biology Open Software Suite (EMBOSS) version 2.2.0 available at www.emboss.org from EMBnet (<http://www.embl.org>). Default settings are used unless otherwise noted. The Needle program in EMBOSS implements the Needleman-Wunsch algorithm.

Needleman, S. B., Wunsch, C. D., *J. Mol. Biol.* 48:443-453 (1970).

10 It is well known to those skilled in the art that implication of alignment algorithms by various programs may result in minor changes in the generated output. These changes include but are not limited to: alignment scores (percent identity, similarity, and gap), display of nonaligned flanking sequence regions, and number assignment to residues. These minor changes in the output of an alignment do not alter the physical characteristics 15 of the sequences or the differences between the sequences, e.g. regions of homology, insertions, or deletions.

Example 1c: RT-PCR Analysis

To detect the presence and tissue distribution of a particular splice variant Reverse Transcription-Polymerase Chain Reaction (RT-PCR) is performed using cDNA generated 20 from a panel of tissue RNAs. See, e.g., Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press (1989) and; Kawasaki ES *et al.*, *PNAS* 85(15):5698 (1988). Total RNA is extracted from a variety of tissues and first strand cDNA is prepared with reverse transcriptase (RT). Each panel includes 23 cDNAs 25 from five cancer types (lung, ovary, breast, colon, and prostate) and normal samples of testis, placenta and fetal brain. Each cancer set is composed of three cancer cDNAs from different donors and one normal pooled sample. Using a standard enzyme kit from BD Bioscience Clontech (Mountain View, CA), the target transcript is detected with

sequence-specific primers designed to only amplify the particular splice variant. The PCR reaction is run on the GeneAmp PCR system 9700 (Applied Biosystem, Foster City, CA) thermocycler under optimal conditions. One of ordinary skill can design appropriate primers and determine optimal conditions. The amplified product is resolved on an 5 agarose gel to detect a band of equivalent size to the predicted RT-PCR product. A band indicated the presence of the splice variant in a sample. The relation of the amplified product to the splice variant was subsequently confirmed by DNA sequencing.

After subcloning, all positively screened clones are sequence verified. The DNA sequence verification results show the splice variant contains the predicted sequence 10 differences in comparison with the reference sequence.

Results for RT-PCR analysis include the sequence DEX ID, Lead Name, Cancer Tissue(s) the transcript was detected in, Normal Tissue(s) the transcript was detected in, the predicted length of the RT-PCR product, and the Confirmed Length of the RT-PCR product.

15 RT-PCR results confirm the presence SEQ ID NO: 1-72 in biologic samples and distinguish between related transcripts.

Example 1d: Secretion Assay

To determine if a protein encoded by a splice variant is secreted from cells a secretion assay is preformed. A pcDNA3.1 clone containing the gene transcript which 20 encodes the variant protein is transfected into 293T cells using the Superfect transfection reagent (Qiagen, Valencia CA). Transfected cells are incubated for 28 hours before the media is collected and immediately spun down to remove any detached cells. The adherent cells are solubilized with lysis buffer (1% NP40, 10mM sodium phosphate pH7.0, and 0.15M NaCl). The lysed cells are collected and spun down and the 25 supernatant extracted as cell lysate. Western immunoblot is carried out in the following manner: 15 μ l of the cell lysate and media are run on 4-12% NuPage Bis-Tris gel (Invitrogen, Carlsbad CA), and blotted onto a PVDF membrane (Invitrogen, Carlsbad CA). The blot is incubated with a polyclonal primary antibody which binds to the variant protein (Imgenex, San Diego CA) and polyclonal goat anti-rabbit-peroxidase secondary 30 antibody (Sigma-Aldrich, St. Louis MO). The blot is developed with the ECL Plus chemiluminescent detection reagent (Amersham BioSciences, Piscataway NJ).

Secretion assay results are indicative of SEQ ID NO: 73-179 being a diagnostic marker and/or therapeutic target for cancer.

Example 2a: Gene Expression Analysis

Custom Microarray Experiment - Cancer

5 Custom oligonucleotide microarrays were provided by Agilent Technologies, Inc. (Palo Alto, CA). The microarrays were fabricated by Agilent using their technology for the *in-situ* synthesis of 60mer oligonucleotides (Hughes, et al. 2001, Nature Biotechnology 19:342-347). The 60mer microarray probes were designed by Agilent, from gene sequences provided by diaDexus, using Agilent proprietary algorithms. Whenever
10 possible two different 60mers were designed for each gene of interest.

All microarray experiments were two-color experiments and were preformed using Agilent-recommended protocols and reagents. Briefly, each microarray was hybridized with cRNAs synthesized from RNA (total RNA for ovarian and prostate, polyA+ RNA for lung, breast and colon samples), isolated from cancer and normal tissues, labeled with
15 fluorescent dyes Cyanine3 (Cy3) or Cyanine5 (Cy5) (NEN Life Science Products, Inc., Boston, MA) using a linear amplification method (Agilent). In each experiment the experimental sample was RNA isolated from cancer tissue from a single individual and the reference sample was a pool of RNA isolated from normal tissues of the same organ as the cancerous tissue (*i.e.* normal ovarian tissue in experiments with ovarian cancer
20 samples). Hybridizations were carried out at 60°C, overnight using Agilent *in-situ* hybridization buffer. Following washing, arrays were scanned with a GenePix 4000B Microarray Scanner (Axon Instruments, Inc., Union City, CA). The resulting images were analyzed with GenePix Pro 3.0 Microarray Acquisition and Analysis Software (Axon).

Data normalization and expression profiling were done with Expressionist
25 software from GeneData Inc. (Daly City, CA/Basel, Switzerland). Gene expression analysis was performed using only experiments that met certain quality criteria. The quality criteria that experiments must meet are a combination of evaluations performed by the Expressionist software and evaluations performed manually using raw and normalized data. To evaluate raw data quality, detection limits (the mean signal for a replicated
30 negative control + 2 Standard Deviations (SD)) for each channel were calculated. The detection limit is a measure of non-specific hybridization. Acceptable detection limits were defined for each dye (<80 for Cy5 and <150 for Cy3). Arrays with poor detection

limits in one or both channels were not analyzed and the experiments were repeated. To evaluate normalized data quality, positive control elements included in the array were utilized. These array features should have a mean ratio of 1 (no differential expression). If these features have a mean ratio of greater than 1.5-fold up or down, the experiments 5 were not analyzed further and were repeated. In addition to traditional scatter plots demonstrating the distribution of signal in each experiment, the Expressionist software also has minimum thresholding criteria that employ user defined parameters to identify quality data. These thresholds include two distinct quality measurements: 1) minimum area percentage, which is a measure of the integrity of each spot and 2) signal to noise 10 ratio, which ensures that the signal being measured is significantly above any background (nonspecific) signal present. Only those features that met the threshold criteria were included in the filtering and analyses carried out by Expressionist. The thresholding settings employed require a minimum area percentage of 60% [(% pixels > background + 2SD)-(% pixels saturated)], and a minimum signal to noise ratio of 2.0 in both channels. 15 By these criteria, very low expressors, saturated features and spots with abnormally high local background were not included in analysis.

Relative expression data was collected from Expressionist based on filtering and clustering analyses. Up-regulated genes were identified using criteria for the percentage of experiments in which the gene is up-regulated by at least 2-fold. In general, up- 20 regulation in ~30% of samples tested was used as a cutoff for filtering.

Two microarray experiments were preformed for each normal and cancer tissue pair. The tissue specific Array Chip for each cancer tissue is a unique microarray specific to that tissue and cancer. The Multi-Cancer Array Chip is a universal microarray that was hybridized with samples from each of the cancers (ovarian, breast, colon, lung, and prostate). See the description below for the experiments specific to the different cancers. 25

Microarray Experiments and Data Tables

BREAST CANCER CHIPS

For breast cancer two different chip designs were evaluated with overlapping sets of a total of 36 samples, comparing the expression patterns of breast cancer derived 30 polyA+ RNA to polyA+ RNA isolated from a pool of 10 normal breast tissues. For the Breast Array Chip, all 36 samples (9 stage I cancers, 23 stage II cancers, 4 stage III cancers) were analyzed. These samples also represented 10 Grade 1/2 and 26 Grade 3

cancers. The histopathologic grades for cancer are classified as follows: GX, cannot be assessed; G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; and G4, undifferentiated. AJCC Cancer Staging Handbook, pp. 9, (5th Ed, 1998).

Samples were further grouped based on the expression patterns of the known breast cancer
5 associated genes Her2 and ER α (10 HER2 up, 26 HER2 not up, 20 ER up and 16 ER not up) and for the Multi-Cancer Array Chip, a subset of 20 of these samples (9 stage I cancers, 8 stage II cancers, 3 stage III cancers) were assessed.

The results for the statistically significant up-regulated genes on the Breast Array Chip are shown in Tables 1 and 2. No results for the statistically significant up-regulated
10 genes on the Multi-Cancer Array Chip are shown. The first two columns of each table contain information about the sequence itself (Seq ID, Oligo Name), the next columns show the results obtained for all (“ALL”) breast cancer samples, cancers corresponding to stage I (“ST1”), stages II and III (“ST2,3”), grades 1 and 2 (“GR1,2”), grade 3 (“GR3”), cancers exhibiting up-regulation of Her2 (“HER2up”) or ER α (“ERup”) or
15 those not exhibiting up-regulation of Her2 (“NOT HER2up”) or ER α (“NOT ERup”). “%up” indicates the percentage of all experiments in which up-regulation of at least 2-fold was observed (n=36 for Colon Array Chip, n=20 for the Multi-Cancer Array Chip), “%valid up” indicates the percentage of experiments with valid expression values in which up-regulation of at least 2-fold was observed.

20 Table 1.

DEX ID	Oligo Name	Mam ALL % up n=36	Mam ALL % valid up n=36	Mam ST1 % up n=9	Mam ST1 % valid up n=9	Mam ST2,3 % up n=27	Mam ST2,3 % valid up n=27	Mam GR1,2 % up n=10	Mam GR1,2 % valid up n=10	Mam GR3 % up n=26	Mam GR3 % valid up n=26
DEX0451_001.nt.1	22403.0	22.2	22.2	22.2	22.2	22.2	22.2	10.0	10.0	26.9	26.9
DEX0451_002.nt.1	19368.0	44.4	45.7	44.4	44.4	44.4	46.2	60.0	60.0	38.5	40.0
DEX0451_002.nt.1	19369.0	22.2	22.2	33.3	33.3	18.5	18.5	30.0	30.0	19.2	19.2
DEX0451_003.nt.1	20531.0	36.1	36.1	11.1	11.1	44.4	44.4	50.0	50.0	30.8	30.8
DEX0451_003.nt.1	20532.0	25.0	26.5	11.1	11.1	29.6	32.0	30.0	30.0	23.1	25.0
DEX0451_004.nt.1	40416.0	2.8	2.8	0.0	0.0	3.7	3.7	0.0	0.0	3.8	3.8
DEX0451_005.nt.1	10310.0	19.4	19.4	11.1	11.1	22.2	22.2	10.0	10.0	23.1	23.1
DEX0451_006.nt.1	12495.0	50.0	52.9	66.7	75.0	44.4	46.2	60.0	66.7	46.2	48.0

DEX0451_007.nt.1	16882.0	27.8	27.8	33.3	33.3	25.9	25.9	40.0	40.0	23.1	23.1
DEX0451_007.nt.1	33254.0	38.9	40.0	55.6	55.6	33.3	34.6	60.0	60.0	30.8	32.0
DEX0451_007.nt.1	33255.0	30.6	30.6	33.3	33.3	29.6	29.6	40.0	40.0	26.9	26.9
DEX0451_007.nt.2	16882.0	27.8	27.8	33.3	33.3	25.9	25.9	40.0	40.0	23.1	23.1
DEX0451_007.nt.2	33254.0	38.9	40.0	55.6	55.6	33.3	34.6	60.0	60.0	30.8	32.0
DEX0451_007.nt.2	33255.0	30.6	30.6	33.3	33.3	29.6	29.6	40.0	40.0	26.9	26.9
DEX0451_007.nt.3	16882.0	27.8	27.8	33.3	33.3	25.9	25.9	40.0	40.0	23.1	23.1
DEX0451_007.nt.3	16883.0	22.2	22.2	33.3	33.3	18.5	18.5	40.0	40.0	15.4	15.4
DEX0451_007.nt.3	33254.0	38.9	40.0	55.6	55.6	33.3	34.6	60.0	60.0	30.8	32.0
DEX0451_007.nt.3	33255.0	30.6	30.6	33.3	33.3	29.6	29.6	40.0	40.0	26.9	26.9
DEX0451_007.nt.4	16882.0	27.8	27.8	33.3	33.3	25.9	25.9	40.0	40.0	23.1	23.1
DEX0451_007.nt.5	33254.0	38.9	40.0	55.6	55.6	33.3	34.6	60.0	60.0	30.8	32.0
DEX0451_007.nt.5	33255.0	30.6	30.6	33.3	33.3	29.6	29.6	40.0	40.0	26.9	26.9
DEX0451_008.nt.1	18463.0	25.0	25.0	22.2	22.2	25.9	25.9	10.0	10.0	30.8	30.8
DEX0451_008.nt.1	19444.0	36.1	36.1	33.3	33.3	37.0	37.0	30.0	30.0	38.5	38.5
DEX0451_008.nt.1	19445.0	33.3	33.3	22.2	22.2	37.0	37.0	30.0	30.0	34.6	34.6
DEX0451_008.nt.1	19448.0	27.8	27.8	22.2	22.2	29.6	29.6	10.0	10.0	34.6	34.6
DEX0451_008.nt.1	31908.0	27.8	27.8	22.2	22.2	29.6	29.6	10.0	10.0	34.6	34.6
DEX0451_009.nt.1	12219.0	8.3	8.3	0.0	0.0	11.1	11.1	0.0	0.0	11.5	11.5
DEX0451_009.nt.1	12220.0	8.3	8.3	0.0	0.0	11.1	11.1	0.0	0.0	11.5	11.5
DEX0451_009.nt.1	13615.0	5.6	5.9	0.0	0.0	7.4	8.0	0.0	0.0	7.7	8.3
DEX0451_011.nt.1	28011.0	27.8	30.3	22.2	28.6	29.6	30.8	20.0	20.0	30.8	34.8
DEX0451_012.nt.1	22451.0	22.2	22.2	22.2	22.2	22.2	22.2	0.0	0.0	30.8	30.8
DEX0451_012.nt.1	22452.0	11.1	11.1	11.1	11.1	11.1	11.1	0.0	0.0	15.4	15.4
DEX0451_013.nt.1	28395.0	13.9	14.7	0.0	0.0	18.5	19.2	30.0	33.3	7.7	8.0
DEX0451_013.nt.1	28396.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_013.nt.2	28395.0	13.9	14.7	0.0	0.0	18.5	19.2	30.0	33.3	7.7	8.0
DEX0451_013.nt.2	28396.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_014.nt.1	16523.0	16.7	17.6	11.1	12.5	18.5	19.2	0.0	0.0	23.1	24.0

DEX0451_015.nt.1	15187.0	30.6	31.4	11.1	11.1	37.0	38.5	40.0	40.0	26.9	28.0
DEX0451_015.nt.1	27235.0	33.3	33.3	11.1	11.1	40.7	40.7	40.0	40.0	30.8	30.8
DEX0451_015.nt.1	27236.0	30.6	30.6	11.1	11.1	37.0	37.0	40.0	40.0	26.9	26.9
DEX0451_015.nt.2	15187.0	30.6	31.4	11.1	11.1	37.0	38.5	40.0	40.0	26.9	28.0
DEX0451_015.nt.2	27235.0	33.3	33.3	11.1	11.1	40.7	40.7	40.0	40.0	30.8	30.8
DEX0451_015.nt.2	27236.0	30.6	30.6	11.1	11.1	37.0	37.0	40.0	40.0	26.9	26.9
DEX0451_016.nt.1	40554.0	13.9	14.3	22.2	22.2	11.1	11.5	50.0	50.0	0.0	0.0
DEX0451_017.nt.1	20531.0	36.1	36.1	11.1	11.1	44.4	44.4	50.0	50.0	30.8	30.8
DEX0451_017.nt.1	20532.0	25.0	26.5	11.1	11.1	29.6	32.0	30.0	30.0	23.1	25.0
DEX0451_018.nt.1	15234.0	25.0	25.0	33.3	33.3	22.2	22.2	50.0	50.0	15.4	15.4
DEX0451_018.nt.1	15980.0	25.0	25.7	33.3	33.3	22.2	23.1	50.0	50.0	15.4	16.0
DEX0451_018.nt.1	15987.0	30.6	30.6	33.3	33.3	29.6	29.6	80.0	80.0	11.5	11.5
DEX0451_018.nt.1	16050.0	25.0	25.0	33.3	33.3	22.2	22.2	50.0	50.0	15.4	15.4
DEX0451_018.nt.1	16055.0	30.6	30.6	33.3	33.3	29.6	29.6	70.0	70.0	15.4	15.4
DEX0451_018.nt.1	16056.0	25.0	25.0	33.3	33.3	22.2	22.2	60.0	60.0	11.5	11.5
DEX0451_018.nt.1	33563.0	25.0	25.0	33.3	33.3	22.2	22.2	60.0	60.0	11.5	11.5
DEX0451_018.nt.2	15234.0	25.0	25.0	33.3	33.3	22.2	22.2	50.0	50.0	15.4	15.4
DEX0451_018.nt.2	15980.0	25.0	25.7	33.3	33.3	22.2	23.1	50.0	50.0	15.4	16.0
DEX0451_018.nt.2	15987.0	30.6	30.6	33.3	33.3	29.6	29.6	80.0	80.0	11.5	11.5
DEX0451_018.nt.2	16050.0	25.0	25.0	33.3	33.3	22.2	22.2	50.0	50.0	15.4	15.4
DEX0451_018.nt.2	16055.0	30.6	30.6	33.3	33.3	29.6	29.6	70.0	70.0	15.4	15.4
DEX0451_018.nt.2	16056.0	25.0	25.0	33.3	33.3	22.2	22.2	60.0	60.0	11.5	11.5
DEX0451_018.nt.2	33563.0	25.0	25.0	33.3	33.3	22.2	22.2	60.0	60.0	11.5	11.5
DEX0451_020.nt.1	32801.0	30.6	30.6	22.2	22.2	33.3	33.3	50.0	50.0	23.1	23.1
DEX0451_021.nt.1	19436.0	2.8	2.9	0.0	0.0	3.7	3.8	0.0	0.0	3.8	4.0
DEX0451_021.nt.1	19437.0	13.9	13.9	22.2	22.2	11.1	11.1	40.0	40.0	3.8	3.8
DEX0451_021.nt.2	19436.0	2.8	2.9	0.0	0.0	3.7	3.8	0.0	0.0	3.8	4.0
DEX0451_021.nt.2	19437.0	13.9	13.9	22.2	22.2	11.1	11.1	40.0	40.0	3.8	3.8
DEX0451_021.nt.3	19436.0	2.8	2.9	0.0	0.0	3.7	3.8	0.0	0.0	3.8	4.0

DEX0451_021.nt.3	19437.0	13.9	13.9	22.2	22.2	11.1	11.1	40.0	40.0	3.8	3.8
DEX0451_022.nt.1	20617.0	30.6	30.6	11.1	11.1	37.0	37.0	40.0	40.0	26.9	26.9
DEX0451_022.nt.1	20618.0	11.1	11.1	0.0	0.0	14.8	14.8	20.0	20.0	7.7	7.7
DEX0451_023.nt.1	18012.0	30.6	31.4	22.2	22.2	33.3	34.6	20.0	20.0	34.6	36.0
DEX0451_023.nt.1	18013.0	27.8	28.6	22.2	22.2	29.6	30.8	20.0	20.0	30.8	32.0
DEX0451_023.nt.1	18016.0	22.2	22.9	22.2	22.2	22.2	23.1	30.0	30.0	19.2	20.0
DEX0451_023.nt.1	18017.0	27.8	28.6	22.2	22.2	29.6	30.8	30.0	30.0	26.9	28.0
DEX0451_023.nt.1	18018.0	27.8	27.8	11.1	11.1	33.3	33.3	10.0	10.0	34.6	34.6
DEX0451_023.nt.1	18019.0	33.3	33.3	11.1	11.1	40.7	40.7	20.0	20.0	38.5	38.5
DEX0451_023.nt.1	28313.0	2.8	3.0	0.0	0.0	3.7	3.8	10.0	10.0	0.0	0.0
DEX0451_023.nt.1	28314.0	2.8	5.0	11.1	25.0	0.0	0.0	0.0	0.0	3.8	7.1
DEX0451_024.nt.1	36510.0	27.8	27.8	22.2	22.2	29.6	29.6	10.0	10.0	34.6	34.6
DEX0451_025.nt.1	21189.0	38.9	40.0	44.4	44.4	37.0	38.5	20.0	20.0	46.2	48.0
DEX0451_026.nt.1	30171.0	33.3	33.3	22.2	22.2	37.0	37.0	30.0	30.0	34.6	34.6
DEX0451_026.nt.1	30172.0	19.4	19.4	11.1	11.1	22.2	22.2	10.0	10.0	23.1	23.1
DEX0451_026.nt.2	30171.0	33.3	33.3	22.2	22.2	37.0	37.0	30.0	30.0	34.6	34.6
DEX0451_026.nt.2	30172.0	19.4	19.4	11.1	11.1	22.2	22.2	10.0	10.0	23.1	23.1
DEX0451_027.nt.1	13999.0	2.8	2.9	0.0	0.0	3.7	3.8	0.0	0.0	3.8	3.8
DEX0451_027.nt.1	14001.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_027.nt.1	20396.0	5.6	5.6	11.1	11.1	3.7	3.7	0.0	0.0	7.7	7.7
DEX0451_027.nt.1	31768.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_027.nt.1	31769.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_028.nt.1	9670.0	11.1	11.4	11.1	11.1	11.1	11.5	10.0	10.0	11.5	12.0
DEX0451_029.nt.1	37563.0	19.4	19.4	11.1	11.1	22.2	22.2	40.0	40.0	11.5	11.5
DEX0451_030.nt.1	34949.0	27.8	27.8	33.3	33.3	25.9	25.9	30.0	30.0	26.9	26.9
DEX0451_032.nt.1	19190.0	19.4	19.4	22.2	22.2	18.5	18.5	40.0	40.0	11.5	11.5
DEX0451_032.nt.1	19191.0	19.4	19.4	22.2	22.2	18.5	18.5	40.0	40.0	11.5	11.5
DEX0451_032.nt.1	19246.0	11.1	13.8	22.2	22.2	7.4	10.0	30.0	37.5	3.8	4.8
DEX0451_032.nt.1	19247.0	5.6	20.0	0.0	0.0	7.4	28.6	10.0	50.0	3.8	12.5

DEX0451_032.nt.1	19262.0	5.6	25.0	0.0	0.0	7.4	25.0	10.0	50.0	3.8	16.7
DEX0451_032.nt.1	19332.0	8.3	13.6	11.1	14.3	7.4	13.3	20.0	33.3	3.8	6.2
DEX0451_032.nt.1	19333.0	11.1	17.4	22.2	25.0	7.4	13.3	30.0	42.9	3.8	6.2
DEX0451_032.nt.1	19387.0	19.4	19.4	22.2	22.2	18.5	18.5	40.0	40.0	11.5	11.5
DEX0451_032.nt.2	19248.0	19.4	19.4	22.2	22.2	18.5	18.5	30.0	30.0	15.4	15.4
DEX0451_032.nt.2	19250.0	16.7	16.7	22.2	22.2	14.8	14.8	30.0	30.0	11.5	11.5
DEX0451_032.nt.2	19260.0	16.7	16.7	22.2	22.2	14.8	14.8	30.0	30.0	11.5	11.5
DEX0451_032.nt.2	19265.0	19.4	19.4	22.2	22.2	18.5	18.5	30.0	30.0	15.4	15.4
DEX0451_032.nt.3	19246.0	11.1	13.8	22.2	22.2	7.4	10.0	30.0	37.5	3.8	4.8
DEX0451_032.nt.3	19247.0	5.6	20.0	0.0	0.0	7.4	28.6	10.0	50.0	3.8	12.5
DEX0451_032.nt.3	19262.0	5.6	25.0	0.0	0.0	7.4	25.0	10.0	50.0	3.8	16.7
DEX0451_032.nt.3	19332.0	8.3	13.6	11.1	14.3	7.4	13.3	20.0	33.3	3.8	6.2
DEX0451_032.nt.3	19333.0	11.1	17.4	22.2	25.0	7.4	13.3	30.0	42.9	3.8	6.2
DEX0451_032.nt.4	19246.0	11.1	13.8	22.2	22.2	7.4	10.0	30.0	37.5	3.8	4.8
DEX0451_032.nt.4	19247.0	5.6	20.0	0.0	0.0	7.4	28.6	10.0	50.0	3.8	12.5
DEX0451_032.nt.4	19262.0	5.6	25.0	0.0	0.0	7.4	25.0	10.0	50.0	3.8	16.7
DEX0451_032.nt.4	19332.0	8.3	13.6	11.1	14.3	7.4	13.3	20.0	33.3	3.8	6.2
DEX0451_032.nt.4	19333.0	11.1	17.4	22.2	25.0	7.4	13.3	30.0	42.9	3.8	6.2
DEX0451_032.nt.5	19191.0	19.4	19.4	22.2	22.2	18.5	18.5	40.0	40.0	11.5	11.5
DEX0451_032.nt.5	19194.0	8.3	8.3	0.0	0.0	11.1	11.1	0.0	0.0	11.5	11.5
DEX0451_032.nt.5	19248.0	19.4	19.4	22.2	22.2	18.5	18.5	30.0	30.0	15.4	15.4
DEX0451_032.nt.5	19250.0	16.7	16.7	22.2	22.2	14.8	14.8	30.0	30.0	11.5	11.5
DEX0451_032.nt.5	19260.0	16.7	16.7	22.2	22.2	14.8	14.8	30.0	30.0	11.5	11.5
DEX0451_032.nt.5	19265.0	19.4	19.4	22.2	22.2	18.5	18.5	30.0	30.0	15.4	15.4
DEX0451_032.nt.6	19190.0	19.4	19.4	22.2	22.2	18.5	18.5	40.0	40.0	11.5	11.5
DEX0451_032.nt.6	19191.0	19.4	19.4	22.2	22.2	18.5	18.5	40.0	40.0	11.5	11.5
DEX0451_032.nt.6	19194.0	8.3	8.3	0.0	0.0	11.1	11.1	0.0	0.0	11.5	11.5
DEX0451_032.nt.6	19246.0	11.1	13.8	22.2	22.2	7.4	10.0	30.0	37.5	3.8	4.8
DEX0451_032.nt.6	19247.0	5.6	20.0	0.0	0.0	7.4	28.6	10.0	50.0	3.8	12.5

DEX0451_032.nt.6	19262.0	5.6	25.0	0.0	0.0	7.4	25.0	10.0	50.0	3.8	16.7
DEX0451_032.nt.6	19332.0	8.3	13.6	11.1	14.3	7.4	13.3	20.0	33.3	3.8	6.2
DEX0451_032.nt.6	19333.0	11.1	17.4	22.2	25.0	7.4	13.3	30.0	42.9	3.8	6.2
DEX0451_032.nt.6	19387.0	19.4	19.4	22.2	22.2	18.5	18.5	40.0	40.0	11.5	11.5
DEX0451_033.nt.1	12500.0	19.4	29.2	22.2	28.6	18.5	29.4	0.0	0.0	26.9	38.9
DEX0451_033.nt.1	12505.0	19.4	19.4	11.1	11.1	22.2	22.2	10.0	10.0	23.1	23.1
DEX0451_033.nt.1	12506.0	19.4	19.4	11.1	11.1	22.2	22.2	20.0	20.0	19.2	19.2
DEX0451_033.nt.1	33560.0	25.0	29.0	22.2	25.0	25.9	30.4	10.0	12.5	30.8	34.8
DEX0451_033.nt.1	33561.0	13.9	38.5	22.2	66.7	11.1	30.0	10.0	50.0	15.4	36.4
DEX0451_033.nt.2	12500.0	19.4	29.2	22.2	28.6	18.5	29.4	0.0	0.0	26.9	38.9
DEX0451_033.nt.2	33560.0	25.0	29.0	22.2	25.0	25.9	30.4	10.0	12.5	30.8	34.8
DEX0451_033.nt.2	33561.0	13.9	38.5	22.2	66.7	11.1	30.0	10.0	50.0	15.4	36.4
DEX0451_034.nt.1	14003.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_034.nt.1	14004.0	25.0	25.0	44.4	44.4	18.5	18.5	20.0	20.0	26.9	26.9
DEX0451_034.nt.1	27151.0	22.2	22.2	44.4	44.4	14.8	14.8	20.0	20.0	23.1	23.1
DEX0451_034.nt.1	27152.0	22.2	22.2	44.4	44.4	14.8	14.8	30.0	30.0	19.2	19.2
DEX0451_036.nt.1	23858.0	61.1	61.1	55.6	55.6	63.0	63.0	70.0	70.0	57.7	57.7
DEX0451_036.nt.1	23859.0	61.1	61.1	55.6	55.6	63.0	63.0	70.0	70.0	57.7	57.7
DEX0451_036.nt.1	37858.0	58.3	58.3	44.4	44.4	63.0	63.0	70.0	70.0	53.8	53.8
DEX0451_036.nt.2	23858.0	61.1	61.1	55.6	55.6	63.0	63.0	70.0	70.0	57.7	57.7
DEX0451_036.nt.2	23859.0	61.1	61.1	55.6	55.6	63.0	63.0	70.0	70.0	57.7	57.7
DEX0451_036.nt.2	37858.0	58.3	58.3	44.4	44.4	63.0	63.0	70.0	70.0	53.8	53.8
DEX0451_036.nt.3	23858.0	61.1	61.1	55.6	55.6	63.0	63.0	70.0	70.0	57.7	57.7
DEX0451_036.nt.3	23859.0	61.1	61.1	55.6	55.6	63.0	63.0	70.0	70.0	57.7	57.7
DEX0451_036.nt.3	37858.0	58.3	58.3	44.4	44.4	63.0	63.0	70.0	70.0	53.8	53.8
DEX0451_037.nt.1	15045.0	30.6	30.6	33.3	33.3	29.6	29.6	40.0	40.0	26.9	26.9
DEX0451_037.nt.1	15066.0	33.3	33.3	22.2	22.2	37.0	37.0	40.0	40.0	30.8	30.8
DEX0451_037.nt.2	15044.0	25.0	25.0	22.2	22.2	25.9	25.9	30.0	30.0	23.1	23.1
DEX0451_037.nt.2	15045.0	30.6	30.6	33.3	33.3	29.6	29.6	40.0	40.0	26.9	26.9

DEX0451_037.nt.2	15062.0	33.3	33.3	22.2	22.2	37.0	37.0	40.0	40.0	30.8	30.8
DEX0451_037.nt.2	15063.0	27.8	30.3	22.2	25.0	29.6	32.0	40.0	40.0	23.1	26.1
DEX0451_037.nt.2	15066.0	33.3	33.3	22.2	22.2	37.0	37.0	40.0	40.0	30.8	30.8
DEX0451_037.nt.2	33432.0	27.8	27.8	22.2	22.2	29.6	29.6	30.0	30.0	26.9	26.9
DEX0451_037.nt.3	15044.0	25.0	25.0	22.2	22.2	25.9	25.9	30.0	30.0	23.1	23.1
DEX0451_037.nt.3	15045.0	30.6	30.6	33.3	33.3	29.6	29.6	40.0	40.0	26.9	26.9
DEX0451_037.nt.3	15062.0	33.3	33.3	22.2	22.2	37.0	37.0	40.0	40.0	30.8	30.8
DEX0451_037.nt.3	15063.0	27.8	30.3	22.2	25.0	29.6	32.0	40.0	40.0	23.1	26.1
DEX0451_037.nt.3	15066.0	33.3	33.3	22.2	22.2	37.0	37.0	40.0	40.0	30.8	30.8
DEX0451_037.nt.3	33432.0	27.8	27.8	22.2	22.2	29.6	29.6	30.0	30.0	26.9	26.9
DEX0451_037.nt.4	15044.0	25.0	25.0	22.2	22.2	25.9	25.9	30.0	30.0	23.1	23.1
DEX0451_037.nt.4	15045.0	30.6	30.6	33.3	33.3	29.6	29.6	40.0	40.0	26.9	26.9
DEX0451_037.nt.4	15066.0	33.3	33.3	22.2	22.2	37.0	37.0	40.0	40.0	30.8	30.8
DEX0451_037.nt.4	15071.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_037.nt.4	33432.0	27.8	27.8	22.2	22.2	29.6	29.6	30.0	30.0	26.9	26.9
DEX0451_037.nt.5	15062.0	33.3	33.3	22.2	22.2	37.0	37.0	40.0	40.0	30.8	30.8
DEX0451_037.nt.5	15063.0	27.8	30.3	22.2	25.0	29.6	32.0	40.0	40.0	23.1	26.1

Table 2.

DEX ID	Oligo Name	Mam HER2up %up n=10	Mam HER2up %valid up n=10	Mam NOT HER2up %up n=26	Mam NOT HER2up %valid up n=26	Mam ERup %up n=20	Mam ERup %valid up n=20	Mam NOT ERup %up n=16	Mam NOT ERup %valid up n=16
DEX0451_001.nt.1	22403.0	20.0	20.0	23.1	23.1	5.0	5.0	43.8	43.8
DEX0451_002.nt.1	19368.0	60.0	66.7	38.5	38.5	60.0	60.0	25.0	26.7
DEX0451_002.nt.1	19369.0	30.0	30.0	19.2	19.2	30.0	30.0	12.5	12.5
DEX0451_003.nt.1	20531.0	30.0	30.0	38.5	38.5	60.0	60.0	6.2	6.2
DEX0451_003.nt.1	20532.0	10.0	11.1	30.8	32.0	40.0	42.1	6.2	6.7
DEX0451_004.nt.1	40416.0	0.0	0.0	3.8	3.8	5.0	5.0	0.0	0.0
DEX0451_005.nt.1	10310.0	30.0	30.0	15.4	15.4	10.0	10.0	31.2	31.2
DEX0451_006.nt.1	12495.0	30.0	30.0	57.7	62.5	60.0	66.7	37.5	37.5
DEX0451_007.nt.1	16882.0	10.0	10.0	34.6	34.6	30.0	30.0	25.0	25.0
DEX0451_007.nt.1	33254.0	20.0	20.0	46.2	48.0	40.0	42.1	37.5	37.5
DEX0451_007.nt.1	33255.0	10.0	10.0	38.5	38.5	30.0	30.0	31.2	31.2
DEX0451_007.nt.2	16882.0	10.0	10.0	34.6	34.6	30.0	30.0	25.0	25.0
DEX0451_007.nt.2	33254.0	20.0	20.0	46.2	48.0	40.0	42.1	37.5	37.5
DEX0451_007.nt.2	33255.0	10.0	10.0	38.5	38.5	30.0	30.0	31.2	31.2
DEX0451_007.nt.3	16882.0	10.0	10.0	34.6	34.6	30.0	30.0	25.0	25.0
DEX0451_007.nt.3	16883.0	10.0	10.0	26.9	26.9	25.0	25.0	18.8	18.8

DEX0451_007.nt.3	33254.0	20.0	20.0	46.2	48.0	40.0	42.1	37.5	37.5
DEX0451_007.nt.3	33255.0	10.0	10.0	38.5	38.5	30.0	30.0	31.2	31.2
DEX0451_007.nt.4	16882.0	10.0	10.0	34.6	34.6	30.0	30.0	25.0	25.0
DEX0451_007.nt.5	33254.0	20.0	20.0	46.2	48.0	40.0	42.1	37.5	37.5
DEX0451_007.nt.5	33255.0	10.0	10.0	38.5	38.5	30.0	30.0	31.2	31.2
DEX0451_008.nt.1	18463.0	10.0	10.0	30.8	30.8	15.0	15.0	37.5	37.5
DEX0451_008.nt.1	19444.0	20.0	20.0	42.3	42.3	30.0	30.0	43.8	43.8
DEX0451_008.nt.1	19445.0	20.0	20.0	38.5	38.5	30.0	30.0	37.5	37.5
DEX0451_008.nt.1	19448.0	20.0	20.0	30.8	30.8	10.0	10.0	50.0	50.0
DEX0451_008.nt.1	31908.0	10.0	10.0	34.6	34.6	15.0	15.0	43.8	43.8
DEX0451_009.nt.1	12219.0	30.0	30.0	0.0	0.0	10.0	10.0	6.2	6.2
DEX0451_009.nt.1	12220.0	30.0	30.0	0.0	0.0	10.0	10.0	6.2	6.2
DEX0451_009.nt.1	13615.0	20.0	22.2	0.0	0.0	5.0	5.0	6.2	7.1
DEX0451_011.nt.1	28011.0	10.0	11.1	34.6	37.5	30.0	31.6	25.0	28.6
DEX0451_012.nt.1	22451.0	10.0	10.0	26.9	26.9	15.0	15.0	31.2	31.2
DEX0451_012.nt.1	22452.0	10.0	10.0	11.5	11.5	5.0	5.0	18.8	18.8
DEX0451_013.nt.1	28395.0	40.0	44.4	3.8	4.0	20.0	21.1	6.2	6.7
DEX0451_013.nt.1	28396.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_013.nt.2	28395.0	40.0	44.4	3.8	4.0	20.0	21.1	6.2	6.7
DEX0451_013.nt.2	28396.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_014.nt.1	16523.0	20.0	20.0	15.4	16.7	0.0	0.0	37.5	40.0
DEX0451_015.nt.1	15187.0	50.0	50.0	23.1	24.0	35.0	36.8	25.0	25.0
DEX0451_015.nt.1	27235.0	60.0	60.0	23.1	23.1	40.0	40.0	25.0	25.0
DEX0451_015.nt.1	27236.0	60.0	60.0	19.2	19.2	35.0	35.0	25.0	25.0
DEX0451_015.nt.2	15187.0	50.0	50.0	23.1	24.0	35.0	36.8	25.0	25.0
DEX0451_015.nt.2	27235.0	60.0	60.0	23.1	23.1	40.0	40.0	25.0	25.0
DEX0451_015.nt.2	27236.0	60.0	60.0	19.2	19.2	35.0	35.0	25.0	25.0
DEX0451_016.nt.1	40554.0	20.0	20.0	11.5	12.0	25.0	26.3	0.0	0.0
DEX0451_017.nt.1	20531.0	30.0	30.0	38.5	38.5	60.0	60.0	6.2	6.2
DEX0451_017.nt.1	20532.0	10.0	11.1	30.8	32.0	40.0	42.1	6.2	6.7
DEX0451_018.nt.1	15234.0	40.0	40.0	19.2	19.2	40.0	40.0	6.2	6.2
DEX0451_018.nt.1	15980.0	40.0	40.0	19.2	20.0	40.0	40.0	6.2	6.7
DEX0451_018.nt.1	15987.0	50.0	50.0	23.1	23.1	55.0	55.0	0.0	0.0
DEX0451_018.nt.1	16050.0	40.0	40.0	19.2	19.2	40.0	40.0	6.2	6.2
DEX0451_018.nt.1	16055.0	50.0	50.0	23.1	23.1	50.0	50.0	6.2	6.2
DEX0451_018.nt.1	16056.0	40.0	40.0	19.2	19.2	45.0	45.0	0.0	0.0
DEX0451_018.nt.1	33563.0	40.0	40.0	19.2	19.2	45.0	45.0	0.0	0.0
DEX0451_018.nt.2	15234.0	40.0	40.0	19.2	19.2	40.0	40.0	6.2	6.2
DEX0451_018.nt.2	15980.0	40.0	40.0	19.2	20.0	40.0	40.0	6.2	6.7
DEX0451_018.nt.2	15987.0	50.0	50.0	23.1	23.1	55.0	55.0	0.0	0.0
DEX0451_018.nt.2	16050.0	40.0	40.0	19.2	19.2	40.0	40.0	6.2	6.2
DEX0451_018.nt.2	16055.0	50.0	50.0	23.1	23.1	50.0	50.0	6.2	6.2
DEX0451_018.nt.2	16056.0	40.0	40.0	19.2	19.2	45.0	45.0	0.0	0.0
DEX0451_018.nt.2	33563.0	40.0	40.0	19.2	19.2	45.0	45.0	0.0	0.0
DEX0451_020.nt.1	32801.0	20.0	20.0	34.6	34.6	40.0	40.0	18.8	18.8
DEX0451_021.nt.1	19436.0	0.0	0.0	3.8	4.0	0.0	0.0	6.2	6.7
DEX0451_021.nt.1	19437.0	20.0	20.0	11.5	11.5	20.0	20.0	6.2	6.2
DEX0451_021.nt.2	19436.0	0.0	0.0	3.8	4.0	0.0	0.0	6.2	6.7
DEX0451_021.nt.2	19437.0	20.0	20.0	11.5	11.5	20.0	20.0	6.2	6.2
DEX0451_021.nt.3	19436.0	0.0	0.0	3.8	4.0	0.0	0.0	6.2	6.7
DEX0451_021.nt.3	19437.0	20.0	20.0	11.5	11.5	20.0	20.0	6.2	6.2
DEX0451_022.nt.1	20617.0	20.0	20.0	34.6	34.6	30.0	30.0	31.2	31.2
DEX0451_022.nt.1	20618.0	10.0	10.0	11.5	11.5	10.0	10.0	12.5	12.5
DEX0451_023.nt.1	18012.0	20.0	22.2	34.6	34.6	20.0	21.1	43.8	43.8
DEX0451_023.nt.1	18013.0	20.0	22.2	30.8	30.8	20.0	21.1	37.5	37.5
DEX0451_023.nt.1	18016.0	20.0	20.0	23.1	24.0	15.0	15.8	31.2	31.2
DEX0451_023.nt.1	18017.0	20.0	22.2	30.8	30.8	25.0	26.3	31.2	31.2

DEX0451_023.nt.1	18018.0	20.0	20.0	30.8	30.8	15.0	15.0	43.8	43.8
DEX0451_023.nt.1	18019.0	20.0	20.0	38.5	38.5	20.0	20.0	50.0	50.0
DEX0451_023.nt.1	28313.0	10.0	11.1	0.0	0.0	5.0	5.6	0.0	0.0
DEX0451_023.nt.1	28314.0	0.0	0.0	3.8	5.9	0.0	0.0	6.2	10.0
DEX0451_024.nt.1	36510.0	30.0	30.0	26.9	26.9	25.0	25.0	31.2	31.2
DEX0451_025.nt.1	21189.0	30.0	33.3	42.3	42.3	20.0	21.1	62.5	62.5
DEX0451_026.nt.1	30171.0	40.0	40.0	30.8	30.8	30.0	30.0	37.5	37.5
DEX0451_026.nt.1	30172.0	30.0	30.0	15.4	15.4	10.0	10.0	31.2	31.2
DEX0451_026.nt.2	30171.0	40.0	40.0	30.8	30.8	30.0	30.0	37.5	37.5
DEX0451_026.nt.2	30172.0	30.0	30.0	15.4	15.4	10.0	10.0	31.2	31.2
DEX0451_027.nt.1	13999.0	10.0	10.0	0.0	0.0	0.0	0.0	6.2	6.2
DEX0451_027.nt.1	14001.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_027.nt.1	20396.0	10.0	10.0	3.8	3.8	0.0	0.0	12.5	12.5
DEX0451_027.nt.1	31768.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_027.nt.1	31769.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_028.nt.1	9670.0	40.0	40.0	0.0	0.0	15.0	15.8	6.2	6.2
DEX0451_029.nt.1	37563.0	30.0	30.0	15.4	15.4	25.0	25.0	12.5	12.5
DEX0451_030.nt.1	34949.0	30.0	30.0	26.9	26.9	20.0	20.0	37.5	37.5
DEX0451_032.nt.1	19190.0	10.0	10.0	23.1	23.1	35.0	35.0	0.0	0.0
DEX0451_032.nt.1	19191.0	10.0	10.0	23.1	23.1	35.0	35.0	0.0	0.0
DEX0451_032.nt.1	19246.0	10.0	12.5	11.5	14.3	20.0	26.7	0.0	0.0
DEX0451_032.nt.1	19247.0	10.0	33.3	3.8	14.3	10.0	28.6	0.0	0.0
DEX0451_032.nt.1	19262.0	10.0	50.0	3.8	16.7	10.0	28.6	0.0	0.0
DEX0451_032.nt.1	19332.0	10.0	14.3	7.7	13.3	15.0	23.1	0.0	0.0
DEX0451_032.nt.1	19333.0	10.0	14.3	11.5	18.8	20.0	28.6	0.0	0.0
DEX0451_032.nt.1	19387.0	10.0	10.0	23.1	23.1	35.0	35.0	0.0	0.0
DEX0451_032.nt.2	19248.0	10.0	10.0	23.1	23.1	30.0	30.0	6.2	6.2
DEX0451_032.nt.2	19250.0	10.0	10.0	19.2	19.2	30.0	30.0	0.0	0.0
DEX0451_032.nt.2	19260.0	10.0	10.0	19.2	19.2	30.0	30.0	0.0	0.0
DEX0451_032.nt.2	19265.0	10.0	10.0	23.1	23.1	30.0	30.0	6.2	6.2
DEX0451_032.nt.3	19246.0	10.0	12.5	11.5	14.3	20.0	26.7	0.0	0.0
DEX0451_032.nt.3	19247.0	10.0	33.3	3.8	14.3	10.0	28.6	0.0	0.0
DEX0451_032.nt.3	19262.0	10.0	50.0	3.8	16.7	10.0	28.6	0.0	0.0
DEX0451_032.nt.3	19332.0	10.0	14.3	7.7	13.3	15.0	23.1	0.0	0.0
DEX0451_032.nt.3	19333.0	10.0	14.3	11.5	18.8	20.0	28.6	0.0	0.0
DEX0451_032.nt.4	19246.0	10.0	12.5	11.5	14.3	20.0	26.7	0.0	0.0
DEX0451_032.nt.4	19247.0	10.0	33.3	3.8	14.3	10.0	28.6	0.0	0.0
DEX0451_032.nt.4	19262.0	10.0	50.0	3.8	16.7	10.0	28.6	0.0	0.0
DEX0451_032.nt.4	19332.0	10.0	14.3	7.7	13.3	15.0	23.1	0.0	0.0
DEX0451_032.nt.4	19333.0	10.0	14.3	11.5	18.8	20.0	28.6	0.0	0.0
DEX0451_032.nt.5	19191.0	10.0	10.0	23.1	23.1	35.0	35.0	0.0	0.0
DEX0451_032.nt.5	19194.0	10.0	10.0	7.7	7.7	15.0	15.0	0.0	0.0
DEX0451_032.nt.5	19248.0	10.0	10.0	23.1	23.1	30.0	30.0	6.2	6.2
DEX0451_032.nt.5	19250.0	10.0	10.0	19.2	19.2	30.0	30.0	0.0	0.0
DEX0451_032.nt.5	19260.0	10.0	10.0	19.2	19.2	30.0	30.0	0.0	0.0
DEX0451_032.nt.5	19265.0	10.0	10.0	23.1	23.1	30.0	30.0	6.2	6.2
DEX0451_032.nt.6	19190.0	10.0	10.0	23.1	23.1	35.0	35.0	0.0	0.0
DEX0451_032.nt.6	19191.0	10.0	10.0	23.1	23.1	35.0	35.0	0.0	0.0
DEX0451_032.nt.6	19194.0	10.0	10.0	7.7	7.7	15.0	15.0	0.0	0.0
DEX0451_032.nt.6	19246.0	10.0	12.5	11.5	14.3	20.0	26.7	0.0	0.0
DEX0451_032.nt.6	19247.0	10.0	33.3	3.8	14.3	10.0	28.6	0.0	0.0
DEX0451_032.nt.6	19262.0	10.0	50.0	3.8	16.7	10.0	28.6	0.0	0.0
DEX0451_032.nt.6	19332.0	10.0	14.3	7.7	13.3	15.0	23.1	0.0	0.0
DEX0451_032.nt.6	19333.0	10.0	14.3	11.5	18.8	20.0	28.6	0.0	0.0
DEX0451_032.nt.6	19387.0	10.0	10.0	23.1	23.1	35.0	35.0	0.0	0.0
DEX0451_033.nt.1	12500.0	40.0	57.1	11.5	17.6	5.0	6.7	37.5	66.7
DEX0451_033.nt.1	12505.0	30.0	30.0	15.4	15.4	5.0	5.0	37.5	37.5

DEX0451_033.nt.1	12506.0	30.0	30.0	15.4	15.4	10.0	10.0	31.2	31.2
DEX0451_033.nt.1	33560.0	50.0	62.5	15.4	17.4	10.0	11.1	43.8	53.8
DEX0451_033.nt.1	33561.0	20.0	50.0	11.5	33.3	5.0	12.5	25.0	80.0
DEX0451_033.nt.2	12500.0	40.0	57.1	11.5	17.6	5.0	6.7	37.5	66.7
DEX0451_033.nt.2	33560.0	50.0	62.5	15.4	17.4	10.0	11.1	43.8	53.8
DEX0451_033.nt.2	33561.0	20.0	50.0	11.5	33.3	5.0	12.5	25.0	80.0
DEX0451_034.nt.1	14003.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_034.nt.1	14004.0	20.0	20.0	26.9	26.9	35.0	35.0	12.5	12.5
DEX0451_034.nt.1	27151.0	20.0	20.0	23.1	23.1	30.0	30.0	12.5	12.5
DEX0451_034.nt.1	27152.0	10.0	10.0	26.9	26.9	40.0	40.0	0.0	0.0
DEX0451_036.nt.1	23858.0	60.0	60.0	61.5	61.5	75.0	75.0	43.8	43.8
DEX0451_036.nt.1	23859.0	60.0	60.0	61.5	61.5	75.0	75.0	43.8	43.8
DEX0451_036.nt.1	37858.0	40.0	40.0	65.4	65.4	70.0	70.0	43.8	43.8
DEX0451_036.nt.2	23858.0	60.0	60.0	61.5	61.5	75.0	75.0	43.8	43.8
DEX0451_036.nt.2	23859.0	60.0	60.0	61.5	61.5	75.0	75.0	43.8	43.8
DEX0451_036.nt.2	37858.0	40.0	40.0	65.4	65.4	70.0	70.0	43.8	43.8
DEX0451_036.nt.3	23858.0	60.0	60.0	61.5	61.5	75.0	75.0	43.8	43.8
DEX0451_036.nt.3	23859.0	60.0	60.0	61.5	61.5	75.0	75.0	43.8	43.8
DEX0451_036.nt.3	37858.0	40.0	40.0	65.4	65.4	70.0	70.0	43.8	43.8
DEX0451_037.nt.1	15045.0	30.0	30.0	30.8	30.8	45.0	45.0	12.5	12.5
DEX0451_037.nt.1	15066.0	50.0	50.0	26.9	26.9	50.0	50.0	12.5	12.5
DEX0451_037.nt.2	15044.0	20.0	20.0	26.9	26.9	40.0	40.0	6.2	6.2
DEX0451_037.nt.2	15045.0	30.0	30.0	30.8	30.8	45.0	45.0	12.5	12.5
DEX0451_037.nt.2	15062.0	50.0	50.0	26.9	26.9	50.0	50.0	12.5	12.5
DEX0451_037.nt.2	15063.0	40.0	50.0	23.1	24.0	45.0	45.0	6.2	7.7
DEX0451_037.nt.2	15066.0	50.0	50.0	26.9	26.9	50.0	50.0	12.5	12.5
DEX0451_037.nt.3	23852.0	40.0	40.0	23.1	23.1	45.0	45.0	6.2	6.2
DEX0451_037.nt.3	15044.0	20.0	20.0	26.9	26.9	40.0	40.0	6.2	6.2
DEX0451_037.nt.3	15045.0	30.0	30.0	30.8	30.8	45.0	45.0	12.5	12.5
DEX0451_037.nt.3	15062.0	50.0	50.0	26.9	26.9	50.0	50.0	12.5	12.5
DEX0451_037.nt.3	15063.0	40.0	50.0	23.1	24.0	45.0	45.0	6.2	7.7
DEX0451_037.nt.3	15066.0	50.0	50.0	26.9	26.9	50.0	50.0	12.5	12.5
DEX0451_037.nt.3	33432.0	40.0	40.0	23.1	23.1	45.0	45.0	6.2	6.2
DEX0451_037.nt.4	15044.0	20.0	20.0	26.9	26.9	40.0	40.0	6.2	6.2
DEX0451_037.nt.4	15045.0	30.0	30.0	30.8	30.8	45.0	45.0	12.5	12.5
DEX0451_037.nt.4	15062.0	50.0	50.0	26.9	26.9	50.0	50.0	12.5	12.5
DEX0451_037.nt.4	15063.0	40.0	50.0	23.1	24.0	45.0	45.0	6.2	7.7
DEX0451_037.nt.4	15066.0	50.0	50.0	26.9	26.9	50.0	50.0	12.5	12.5
DEX0451_037.nt.4	15071.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_037.nt.4	33432.0	40.0	40.0	23.1	23.1	45.0	45.0	6.2	6.2
DEX0451_037.nt.5	15062.0	50.0	50.0	26.9	26.9	50.0	50.0	12.5	12.5
DEX0451_037.nt.5	15063.0	40.0	50.0	23.1	24.0	45.0	45.0	6.2	7.7

COLON CANCER CHIPS

For colon cancer two different chip designs were evaluated with overlapping sets of a total of 38 samples, comparing the expression patterns of colon cancer derived polyA+ RNA to polyA+ RNA isolated from a pool of 7 normal colon tissues. For the Colon Array Chip all 38 samples (23 Ascending colon carcinomas and 15 Rectosigmoidal carcinomas including: 5 stage I cancers, 15 stage II cancers, 15 stage III and 2 stage IV cancers, as well as 28 Grade1/2 and 10 Grade 3 cancers) were analyzed. The histopathologic grades for cancer are classified as follows: GX, cannot be assessed; G1, well differentiated; G2, Moderately differentiated; G3, poorly differentiated; and G4,

undifferentiated. AJCC Cancer Staging Handbook, 5th Edition, 1998, page 9. For the Colon Array Chip analysis, samples were further divided into groups based on the expression pattern of the known colon cancer associated gene Thymidilate Synthase (TS) (13 TS up 25 TS not up). The association of TS with advanced colorectal cancer is well documented. Paradiso *et al.*, *Br J Cancer* 82(3):560-7 (2000); Etienne *et al.*, *J Clin Oncol.* 20(12):2832-43 (2002); Aschele *et al.* *Clin Cancer Res.* 6(12):4797-802 (2000). For the Multi-Cancer Array Chip a subset of 27 of these samples (14 Ascending colon carcinomas and 13 Rectosigmoidal carcinomas including: 3 stage I cancers, 9 stage II cancers, 13 stage III and 2 stage IV cancers) were assessed.

The results for the statistically significant up-regulated genes on the Colon Array Chip are shown in Tables 3 and 4. No results for the statistically significant up-regulated genes on the Multi-Cancer Array Chip are shown.

The first two columns of each table contain information about the sequence itself (Seq ID, Oligo Name), the next columns show the results obtained for all ("ALL") the colon samples, ascending colon carcinomas ("ASC"), Rectosigmoidal carcinomas ("RS"), cancers corresponding to stages I and II ("ST1,2"), stages III and IV ("ST3,4"), grades 1 and 2 ("GR1,2"), grade 3 ("GR3"), cancers exhibiting up-regulation of the TS gene ("TSup") or those not exhibiting up-regulation of the TS gene ("NOT TSup"). '%up' indicates the percentage of all experiments in which up-regulation of at least 2-fold was observed n=38 for the Colon Array Chip (n=27 for the Multi-Cancer Array Chip), '%valid up' indicates the percentage of experiments with valid expression values in which up-regulation of at least 2-fold was observed.

Table 3.

DEX ID	Oligo Name	Cln ALL % up n=38	Cln ALL % valid up n=38	Cln ASC % up n=23	Cln ASC % valid up n=23	Cln RS % up n=15	Cln RS % valid up n=15	Cln ST1, 2 % up n=15	Cln ST1, 2 % valid up n=20	Cln ST3, 4 % up n=18	Cln ST3, 4 % valid up n=18
DEX0451_010.nt.1	36158.0	15.8	15.8	13.0	13.0	20.0	20.0	15.0	15.0	16.7	16.7
DEX0451_026.nt.1	9521.0	7.9	7.9	13.0	13.0	0.0	0.0	5.0	5.0	11.1	11.1
DEX0451_028.nt.1	32686.0	5.3	5.7	4.3	4.8	6.7	7.1	5.0	5.6	5.6	5.9
DEX0451_028.nt.1	32687.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_028.nt.1	35234.0	13.2	13.2	13.0	13.0	13.3	13.3	10.0	10.0	16.7	16.7
DEX0451_028.nt.1	35235.0	13.2	13.2	13.0	13.0	13.3	13.3	10.0	10.0	16.7	16.7

DEX0451_028.nt.2	35234.0	13.2	13.2	13.0	13.0	13.3	13.3	10.0	10.0	16.7	16.7
DEX0451_028.nt.2	35235.0	13.2	13.2	13.0	13.0	13.3	13.3	10.0	10.0	16.7	16.7
DEX0451_030.nt.1	34752.0	5.3	5.3	4.3	4.3	6.7	6.7	0.0	0.0	11.1	11.1
DEX0451_030.nt.1	34753.0	7.9	7.9	8.7	8.7	6.7	6.7	5.0	5.0	11.1	11.1
DEX0451_030.nt.2	34752.0	5.3	5.3	4.3	4.3	6.7	6.7	0.0	0.0	11.1	11.1
DEX0451_030.nt.2	34753.0	7.9	7.9	8.7	8.7	6.7	6.7	5.0	5.0	11.1	11.1
DEX0451_033.nt.1	36947.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	36948.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	38489.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	36947.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	36948.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	38489.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_036.nt.1	35114.0	5.3	5.3	8.7	8.7	0.0	0.0	5.0	5.0	5.6	5.6
DEX0451_036.nt.1	35115.0	5.3	5.3	8.7	8.7	0.0	0.0	5.0	5.0	5.6	5.6
DEX0451_036.nt.2	35114.0	5.3	5.3	8.7	8.7	0.0	0.0	5.0	5.0	5.6	5.6
DEX0451_036.nt.2	35115.0	5.3	5.3	8.7	8.7	0.0	0.0	5.0	5.0	5.6	5.6
DEX0451_036.nt.3	35114.0	5.3	5.3	8.7	8.7	0.0	0.0	5.0	5.0	5.6	5.6
DEX0451_036.nt.3	35115.0	5.3	5.3	8.7	8.7	0.0	0.0	5.0	5.0	5.6	5.6
DEX0451_037.nt.2	19356.0	2.6	2.6	0.0	0.0	6.7	6.7	0.0	0.0	5.6	5.6

Table 4.

DEX ID	Oligo Name	Cln GR1,2 %up n=28	Cln GR1,2 %valid up n=28	Cln GR3 %up n=10	Cln GR3 %valid up n=10	Cln TS up %up n=13	Cln TS up %valid n=13	Cln NOT TS up %up n=25	Cln NOT TS up %valid up n=25
DEX0451_010.nt.1	36158.0	17.9	17.9	10.0	10.0	0.0	0.0	24.0	24.0
DEX0451_026.nt.1	9521.0	7.1	7.1	10.0	10.0	15.4	15.4	4.0	4.0
DEX0451_028.nt.1	32686.0	3.6	3.8	10.0	11.1	7.7	7.7	4.0	4.5
DEX0451_028.nt.1	32687.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_028.nt.1	35234.0	10.7	10.7	20.0	20.0	7.7	7.7	16.0	16.0
DEX0451_028.nt.1	35235.0	14.3	14.3	10.0	10.0	15.4	15.4	12.0	12.0
DEX0451_028.nt.2	35234.0	10.7	10.7	20.0	20.0	7.7	7.7	16.0	16.0
DEX0451_028.nt.2	35235.0	14.3	14.3	10.0	10.0	15.4	15.4	12.0	12.0
DEX0451_030.nt.1	34752.0	7.1	7.1	0.0	0.0	7.7	7.7	4.0	4.0
DEX0451_030.nt.1	34753.0	7.1	7.1	10.0	10.0	7.7	7.7	8.0	8.0
DEX0451_030.nt.2	34752.0	7.1	7.1	0.0	0.0	7.7	7.7	4.0	4.0
DEX0451_030.nt.2	34753.0	7.1	7.1	10.0	10.0	7.7	7.7	8.0	8.0

DEX0451_033.nt.1	36947.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	36948.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	38489.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	36947.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	36948.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	38489.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_036.nt.1	35114.0	3.6	3.6	10.0	10.0	7.7	7.7	4.0	4.0	4.0	
DEX0451_036.nt.1	35115.0	3.6	3.6	10.0	10.0	7.7	7.7	4.0	4.0	4.0	
DEX0451_036.nt.2	35114.0	3.6	3.6	10.0	10.0	7.7	7.7	4.0	4.0	4.0	
DEX0451_036.nt.2	35115.0	3.6	3.6	10.0	10.0	7.7	7.7	4.0	4.0	4.0	
DEX0451_036.nt.3	35114.0	3.6	3.6	10.0	10.0	7.7	7.7	4.0	4.0	4.0	
DEX0451_036.nt.3	35115.0	3.6	3.6	10.0	10.0	7.7	7.7	4.0	4.0	4.0	
DEX0451_037.nt.2	19356.0	0.0	0.0	10.0	10.0	7.7	7.7	0.0	0.0	0.0	

LUNG CANCER CHIPS

For lung cancer two different chip designs were evaluated with overlapping sets of a total of 29 samples, comparing the expression patterns of lung cancer derived polyA+

5 RNA to polyA+ RNA isolated from a pool of 12 normal lung tissues. For the Lung Array Chip all 29 samples (15 squamous cell carcinomas and 14 adenocarcinomas including 14 stage I and 15 stage II/III cancers) were analyzed and for the Multi-Cancer Array Chip a subset of 22 of these samples (10 squamous cell carcinomas, 12 adenocarcinomas) were assessed.

10 The results for the statistically significant up-regulated genes on the Lung Array Chip are shown in Table 5. No results for the statistically significant up-regulated genes on the Multi-Cancer Array Chip are shown. The first two columns of each table contain information about the sequence itself (DEX ID, Oligo Name), the next columns show the results obtained for all ("ALL") lung cancer samples, squamous cell carcinomas ("SQ"), adenocarcinomas ("AD"), or cancers corresponding to stage I ("ST1"), or stages II and III ("ST2,3"). '%up' indicates the percentage of all experiments in which up-regulation of at least 2-fold was observed (n=29 for Lung Array Chip, n=22 for Multi-Cancer Array Chip), "%valid up" indicates the percentage of experiments with valid expression values in which up-regulation of at least 2-fold was observed.

15 20 Table 5.

DEX ID	Oligo Name	Lng ALL % up n=29	Lng ALL % valid up n=29	Lng SQ % up n=15	Lng AD % up n=15	Lng AD % valid up n=14	Lng ST1 % up n=14	Lng ST1 % valid up n=14	Lng ST2,3 % up n=15	Lng ST2,3 % valid up n=15	
DEX0451_024.nt.1	5882.0	20.7	20.7	26.7	26.7	14.3	14.3	14.3	14.3	26.7	26.7
DEX0451_029.nt.1	3470.0	6.9	6.9	0.0	0.0	14.3	14.3	14.3	14.3	0.0	0.0

DEX0451_029.nt.1	3471.0	3.4	3.4	0.0	0.0	7.1	7.1	7.1	7.1	0.0	0.0
DEX0451_033.nt.1	5781.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	5782.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	5503.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	5504.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	5781.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	5782.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

OVARIAN CANCER CHIPS

For ovarian cancer two different chip designs were evaluated with overlapping sets of a total of 19 samples, comparing the expression patterns of ovarian cancer derived total RNA to total RNA isolated from a pool of 9 normal ovarian tissues. For the Multi-Cancer Array Chip, all 19 samples (14 invasive carcinomas, 5 low malignant potential samples) were analyzed and for the Ovarian Array Chip, a subset of 17 of these samples (13 invasive carcinomas, 4 low malignant potential samples) were assessed.

The results for the statistically significant up-regulated genes on the Ovarian Array Chip are shown in Table 6. No results for the statistically significant up-regulated genes on the Multi-Cancer Array Chip are shown. The first two columns of each table contain information about the sequence itself (DEX ID, Oligo Name), the next columns show the results obtained for all ("ALL") ovarian cancer samples, invasive carcinomas ("INV") and low malignant potential ("LMP") samples. "%up" indicates the percentage of all experiments in which up-regulation of at least 2-fold was observed (n=19 for the Multi-Cancer Array Chip, n=17 for the Ovarian Array Chip), "%valid up" indicates the percentage of experiments with valid expression values in which up-regulation of at least 2-fold was observed.

Table 6.

DEX ID	Oligo Name	Ovr ALL %up n=17	Ovr ALL %valid up n=17	Ovr INV %up n=13	Ovr INV %valid up n=13	Ovr LMP %up n=4	Ovr LMP %valid up n=4
DEX0451_007.nt.4	20797.01	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_007.nt.4	20797.02	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	9846.01	0.0	0.0	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	9846.02	0.0	0.0	0.0	0.0	0.0	0.0

For prostate cancer three different chip designs were evaluated with overlapping sets of a total of 29 samples, comparing the expression patterns of prostate cancer or benign disease derived total RNA to total RNA isolated from a pool of 35 normal prostate tissues. For the Prostate1 Array and Prostate2 Array Chips all 29 samples (17 prostate cancer samples, 12 non-malignant disease samples) were analyzed. For the Multi-Cancer Array Chip a subset of 28 of these samples (16 prostate cancer samples, 12 non-malignant disease samples) was analyzed.

The results for the statistically significant up-regulated genes on the Prostate1 Array Chip and the Prostate2 Array Chip are shown in Table 7. No results for the 10 statistically significant up-regulated genes on the Multi-Cancer Array Chip are shown. The first two columns of each table contain information about the sequence itself (DEX ID, Oligo Name), the next columns show the results obtained for prostate cancer samples (“CAN”) or non-malignant disease samples (“DIS”). ‘%up’ indicates the percentage of all experiments in which up-regulation of at least 2-fold was observed (n=29 for the Prostate2 15 Array Chip and the Multi-Cancer Array Chip), ‘%valid up’ indicates the percentage of experiments with valid expression values in which up-regulation of at least 2-fold was observed.

Table 7.

DEX ID	Oligo Name	Pro CAN %up n=17	Pro CAN %valid up n=17	Pro DIS %up n=12	Pro DIS %valid up n=12
DEX0451_006.nt.1	27839.01	0.0	0.0	8.3	8.3
DEX0451_006.nt.1	27839.02	0.0	0.0	8.3	8.3
DEX0451_006.nt.1	38183.01	5.9	5.9	8.3	8.3
DEX0451_006.nt.1	38183.02	0.0	0.0	0.0	0.0
DEX0451_006.nt.2	27839.01	0.0	0.0	8.3	8.3
DEX0451_006.nt.2	27839.02	0.0	0.0	8.3	8.3
DEX0451_006.nt.2	38183.01	5.9	5.9	8.3	8.3
DEX0451_006.nt.2	38183.02	0.0	0.0	0.0	0.0
DEX0451_006.nt.3	27839.01	0.0	0.0	8.3	8.3
DEX0451_006.nt.3	27839.02	0.0	0.0	8.3	8.3
DEX0451_006.nt.3	38183.01	5.9	5.9	8.3	8.3
DEX0451_006.nt.3	38183.02	0.0	0.0	0.0	0.0
DEX0451_006.nt.4	27839.01	0.0	0.0	8.3	8.3
DEX0451_006.nt.4	27839.02	0.0	0.0	8.3	8.3
DEX0451_006.nt.4	38183.01	5.9	5.9	8.3	8.3
DEX0451_006.nt.4	38183.02	0.0	0.0	0.0	0.0
DEX0451_006.nt.5	27839.01	0.0	0.0	8.3	8.3
DEX0451_006.nt.5	27839.02	0.0	0.0	8.3	8.3
DEX0451_006.nt.5	38183.01	5.9	5.9	8.3	8.3
DEX0451_006.nt.5	38183.02	0.0	0.0	0.0	0.0
DEX0451_006.nt.6	27839.01	0.0	0.0	8.3	8.3
DEX0451_006.nt.6	27839.02	0.0	0.0	8.3	8.3
DEX0451_006.nt.6	38183.01	5.9	5.9	8.3	8.3

DEX0451_006.nt.6	38183.02	0.0	0.0	0.0	0.0
DEX0451_006.nt.7	27839.01	0.0	0.0	8.3	8.3
DEX0451_006.nt.7	27839.02	0.0	0.0	8.3	8.3
DEX0451_006.nt.7	38183.01	5.9	5.9	8.3	8.3
DEX0451_006.nt.7	38183.02	0.0	0.0	0.0	0.0
DEX0451_006.nt.8	27839.01	0.0	0.0	8.3	8.3
DEX0451_006.nt.8	27839.02	0.0	0.0	8.3	8.3
DEX0451_006.nt.8	38183.01	5.9	5.9	8.3	8.3
DEX0451_006.nt.8	38183.02	0.0	0.0	0.0	0.0
DEX0451_009.nt.1	30679.01	0.0	0.0	0.0	0.0
DEX0451_009.nt.1	30679.02	0.0	0.0	0.0	0.0
DEX0451_009.nt.1	30679.03	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	29721.01	0.0	0.0	0.0	0.0
DEX0451_033.nt.1	29721.02	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	29721.01	0.0	0.0	0.0	0.0
DEX0451_033.nt.2	29721.02	0.0	0.0	0.0	0.0

SEQ ID NO: 1-72 was up-regulated on various tissue microarrays. Accordingly, nucleotide SEQ ID NO: 1-72 or the encoded protein SEQ ID NO: 73-179 may be used as a cancer therapeutic and/or diagnostic target for the tissues in which expression is shown.

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The following table lists the location (Oligo Location) where the microarray oligos (Oligo ID) map on the transcripts (DEX ID) of the present invention. Each Oligo ID may have been printed multiple times on a single chip as replicates. The Oligo Name is an exemplary replicate (e.g. 1000.01) for the Oligo ID (e.g. 1000), and data from other replicates (e.g. 1000.02, 1000.03) may be reported. Additionally, the Array (Chip Name) that each oligo and oligo replicates were printed on is included.

DEX NT ID	Oligo ID	Oligo Name	Chip Name	Oligo Location
DEX0451_001.nt.1	22403	22403.0	Breast array	371-430
DEX0451_002.nt.1	19368	19368.0	Breast array	890-949
DEX0451_002.nt.1	19369	19369.0	Breast array	816-875
DEX0451_003.nt.1	20532	20532.0	Breast array	675-734
DEX0451_003.nt.1	20531	20531.0	Breast array	772-831
DEX0451_004.nt.1	40416	40416.0	Breast array	6-65
DEX0451_005.nt.1	10310	10310.0	Breast array	2608-2667
DEX0451_006.nt.1	12495	12495.0	Breast array	279-338
DEX0451_006.nt.1	27839	27839.02	Prostate1 array	279-338
DEX0451_006.nt.1	38183	38183.02	Prostate1 array	279-338
DEX0451_006.nt.2	12495	12495.0	Breast array	291-350
DEX0451_006.nt.2	27839	27839.02	Prostate1 array	291-350
DEX0451_006.nt.2	38183	38183.02	Prostate1 array	291-350
DEX0451_006.nt.3	27839	27839.02	Prostate1 array	307-366
DEX0451_006.nt.3	38183	38183.02	Prostate1 array	307-366

DEX0451_006.nt.3	12495	12495.0	Breast array	307-366
DEX0451_006.nt.4	27839	27839.02	Prostate1 array	273-332
DEX0451_006.nt.4	12495	12495.0	Breast array	273-332
DEX0451_006.nt.4	38183	38183.02	Prostate1 array	273-332
DEX0451_006.nt.5	12495	12495.0	Breast array	248-307
DEX0451_006.nt.5	27839	27839.02	Prostate1 array	248-307
DEX0451_006.nt.5	38183	38183.02	Prostate1 array	248-307
DEX0451_006.nt.6	12495	12495.0	Breast array	249-308
DEX0451_006.nt.6	27839	27839.02	Prostate1 array	249-308
DEX0451_006.nt.7	12495	12495.0	Breast array	268-327
DEX0451_006.nt.7	27839	27839.02	Prostate1 array	268-327
DEX0451_006.nt.7	38183	38183.02	Prostate1 array	268-327
DEX0451_006.nt.8	27839	27839.02	Prostate1 array	336-395
DEX0451_006.nt.8	12495	12495.0	Breast array	336-395
DEX0451_006.nt.8	38183	38183.02	Prostate1 array	336-395
DEX0451_007.nt.1	33254	33254.0	Breast array	1192-1251
DEX0451_007.nt.1	16882	16882.0	Breast array	425-484
DEX0451_007.nt.1	33255	33255.0	Breast array	1152-1211
DEX0451_007.nt.2	16882	16882.0	Breast array	929-988
DEX0451_007.nt.2	33254	33254.0	Breast array	1696-1755
DEX0451_007.nt.3	16882	16882.0	Breast array	254-313
DEX0451_007.nt.3	33255	33255.0	Breast array	981-1040
DEX0451_007.nt.3	16883	16883.0	Breast array	234-293
DEX0451_007.nt.4	16882	16882.0	Breast array	785-844
DEX0451_007.nt.4	20797	20797.01	Ovarian array	1202-1261
DEX0451_007.nt.5	33254	33254.0	Breast array	363-422
DEX0451_007.nt.5	33255	33255.0	Breast array	323-382
DEX0451_008.nt.1	19444	19444.0	Breast array	618-677
DEX0451_008.nt.1	19445	19445.0	Breast array	586-645
DEX0451_008.nt.1	31908	31908.0	Breast array	298-357
DEX0451_008.nt.1	18463	18463.0	Breast array	401-460
DEX0451_008.nt.1	19448	19448.0	Breast array	129-188
DEX0451_009.nt.1	12220	12220.0	Breast array	4012-4071
DEX0451_009.nt.1	13615	13615.0	Breast array	2029-2088
DEX0451_009.nt.1	12219	12219.0	Breast array	4059-4118
DEX0451_009.nt.1	30679	30679.03	Prostate2 array	3406-3465
DEX0451_010.nt.1	36158	36158.0	Colon array	840-899
DEX0451_011.nt.1	28011	28011.0	Breast array	1046-1105
DEX0451_012.nt.1	22451	22451.0	Breast array	712-771
DEX0451_012.nt.1	22452	22452.0	Breast array	557-616
DEX0451_013.nt.1	28395	28395.0	Breast array	2949-3008
DEX0451_013.nt.1	28396	28396.0	Breast array	2710-2769
DEX0451_013.nt.2	28395	28395.0	Breast array	2318-2377
DEX0451_013.nt.2	28396	28396.0	Breast array	2079-2138
DEX0451_014.nt.1	16523	16523.0	Breast array	1061-1120
DEX0451_015.nt.1	15187	15187.0	Breast array	1314-1373
DEX0451_015.nt.1	27235	27235.0	Breast array	1848-1907
DEX0451_015.nt.1	27236	27236.0	Breast array	1705-1764

DEX0451_015.nt.2	15187	15187.0	Breast array	816-875
DEX0451_015.nt.2	27236	27236.0	Breast array	1207-1266
DEX0451_015.nt.2	27235	27235.0	Breast array	1350-1409
DEX0451_016.nt.1	40554	40554.0	Breast array	802-861
DEX0451_017.nt.1	20532	20532.0	Breast array	677-736
DEX0451_017.nt.1	20531	20531.0	Breast array	774-833
DEX0451_018.nt.1	16056	16056.0	Breast array	2484-2543
DEX0451_018.nt.1	16050	16050.0	Breast array	1245-1304
DEX0451_018.nt.1	15234	15234.0	Breast array	1901-1960
DEX0451_018.nt.1	15980	15980.0	Breast array	1159-1218
DEX0451_018.nt.1	16055	16055.0	Breast array	2543-2602
DEX0451_018.nt.1	33563	33563.0	Breast array	2523-2582
DEX0451_018.nt.1	15987	15987.0	Breast array	2523-2582
DEX0451_018.nt.2	33563	33563.0	Breast array	2690-2749
DEX0451_018.nt.2	16055	16055.0	Breast array	2710-2769
DEX0451_018.nt.2	15980	15980.0	Breast array	1419-1478
DEX0451_018.nt.2	15987	15987.0	Breast array	2690-2749
DEX0451_018.nt.2	16056	16056.0	Breast array	2651-2710
DEX0451_018.nt.2	15234	15234.0	Breast array	2068-2127
DEX0451_018.nt.2	16050	16050.0	Breast array	1505-1564
DEX0451_020.nt.1	32801	32801.0	Breast array	2692-2751
DEX0451_021.nt.1	19437	19437.0	Breast array	630-689
DEX0451_021.nt.1	19436	19436.0	Breast array	686-745
DEX0451_021.nt.2	19437	19437.0	Breast array	630-689
DEX0451_021.nt.2	19436	19436.0	Breast array	686-745
DEX0451_021.nt.3	19437	19437.0	Breast array	540-599
DEX0451_021.nt.3	19436	19436.0	Breast array	596-655
DEX0451_022.nt.1	20618	20618.0	Breast array	1284-1343
DEX0451_022.nt.1	20617	20617.0	Breast array	1399-1458
DEX0451_023.nt.1	18017	18017.0	Breast array	1792-1851
DEX0451_023.nt.1	18016	18016.0	Breast array	1859-1918
DEX0451_023.nt.1	28313	28313.0	Breast array	4052-4111
DEX0451_023.nt.1	18012	18012.0	Breast array	1958-2017
DEX0451_023.nt.1	18013	18013.0	Breast array	1918-1977
DEX0451_023.nt.1	18019	18019.0	Breast array	1555-1614
DEX0451_023.nt.1	28314	28314.0	Breast array	3867-3926
DEX0451_023.nt.1	18018	18018.0	Breast array	1595-1654
DEX0451_024.nt.1	5882	5882.0	Lung array	630-689
DEX0451_024.nt.1	36510	36510.0	Breast array	663-722
DEX0451_025.nt.1	21189	21189.0	Breast array	668-727
DEX0451_026.nt.1	30172	30172.0	Breast array	214-273
DEX0451_026.nt.1	9521	9521.0	Colon array	52-111
DEX0451_026.nt.1	30171	30171.0	Breast array	307-366
DEX0451_026.nt.2	30172	30172.0	Breast array	1314-1373
DEX0451_026.nt.2	9521	9521.0	Colon array	1152-1211
DEX0451_027.nt.1	14001	14001.0	Breast array	2240-2299
DEX0451_027.nt.1	31768	31768.0	Breast array	2420-2479
DEX0451_027.nt.1	20396	20396.0	Breast array	3155-3214
DEX0451_027.nt.1	31769	31769.0	Breast array	2380-2439
DEX0451_027.nt.1	13999	13999.0	Breast array	3175-3234
DEX0451_028.nt.1	32687	32687.0	Colon array	1165-1224
DEX0451_028.nt.1	32686	32686.0	Colon array	1327-1386
DEX0451_028.nt.1	35235	35235.0	Colon array	2085-2144
DEX0451_028.nt.1	35234	35234.0	Colon array	2131-2190
DEX0451_028.nt.1	9670	9670.0	Breast array	2141-2200
DEX0451_028.nt.2	35235	35235.0	Colon array	787-846
DEX0451_028.nt.2	35234	35234.0	Colon array	833-892

DEX0451_028.nt.2	9670	9670.0	Breast array	843-902
DEX0451_029.nt.1	3471	3471.0	Lung array	1239-1298
DEX0451_029.nt.1	3470	3470.0	Lung array	1279-1338
DEX0451_029.nt.1	37563	37563.0	Breast array	1706-1765
DEX0451_030.nt.1	34753	34753.0	Colon array	1085-1144
DEX0451_030.nt.1	34949	34949.0	Breast array	1090-1149
DEX0451_030.nt.1	34752	34752.0	Colon array	1125-1184
DEX0451_030.nt.2	34753	34753.0	Colon array	1353-1412
DEX0451_030.nt.2	34752	34752.0	Colon array	1393-1452
DEX0451_030.nt.2	34949	34949.0	Breast array	1358-1417
DEX0451_032.nt.1	19246	19246.0	Breast array	645-704
DEX0451_032.nt.1	19262	19262.0	Breast array	605-664
DEX0451_032.nt.1	19190	19190.0	Breast array	165-224
DEX0451_032.nt.1	19247	19247.0	Breast array	605-664
DEX0451_032.nt.1	19333	19333.0	Breast array	524-583
DEX0451_032.nt.1	19387	19387.0	Breast array	304-363
DEX0451_032.nt.1	19332	19332.0	Breast array	544-603
DEX0451_032.nt.1	19191	19191.0	Breast array	135-194
DEX0451_032.nt.2	19250	19250.0	Breast array	631-690
DEX0451_032.nt.2	19265	19265.0	Breast array	631-690
DEX0451_032.nt.2	19260	19260.0	Breast array	475-534
DEX0451_032.nt.2	19248	19248.0	Breast array	631-690
DEX0451_032.nt.3	19246	19246.0	Breast array	211-270
DEX0451_032.nt.3	19332	19332.0	Breast array	110-169
DEX0451_032.nt.3	19333	19333.0	Breast array	90-149
DEX0451_032.nt.3	19247	19247.0	Breast array	171-230
DEX0451_032.nt.3	19262	19262.0	Breast array	171-230
DEX0451_032.nt.4	19246	19246.0	Breast array	225-284
DEX0451_032.nt.4	19247	19247.0	Breast array	185-244
DEX0451_032.nt.4	19332	19332.0	Breast array	124-183
DEX0451_032.nt.4	19333	19333.0	Breast array	104-163
DEX0451_032.nt.4	19262	19262.0	Breast array	185-244
DEX0451_032.nt.5	19191	19191.0	Breast array	836-895
DEX0451_032.nt.5	19260	19260.0	Breast array	406-465
DEX0451_032.nt.5	19248	19248.0	Breast array	562-621
DEX0451_032.nt.5	19250	19250.0	Breast array	562-621
DEX0451_032.nt.5	19265	19265.0	Breast array	562-621
DEX0451_032.nt.5	19194	19194.0	Breast array	712-771
DEX0451_032.nt.6	19333	19333.0	Breast array	1199-1258
DEX0451_032.nt.6	19191	19191.0	Breast array	810-869
DEX0451_032.nt.6	19262	19262.0	Breast array	1280-1339
DEX0451_032.nt.6	19190	19190.0	Breast array	840-899
DEX0451_032.nt.6	19246	19246.0	Breast array	1320-1379
DEX0451_032.nt.6	19387	19387.0	Breast array	979-1038
DEX0451_032.nt.6	19194	19194.0	Breast array	686-745
DEX0451_032.nt.6	19247	19247.0	Breast array	1280-1339
DEX0451_032.nt.6	19332	19332.0	Breast array	1219-1278
DEX0451_033.nt.1	36948	36948.0	Colon array	734-793
DEX0451_033.nt.1	12505	12505.0	Breast array	336-395
DEX0451_033.nt.1	5782	5782.0	Lung array	736-795
DEX0451_033.nt.1	12506	12506.0	Breast array	316-375
DEX0451_033.nt.1	36947	36947.0	Colon array	777-836
DEX0451_033.nt.1	9846	9846.01	Ovarian array	317-376
DEX0451_033.nt.1	29721	29721.02	ProstateL array	777-836
DEX0451_033.nt.1	38489	38489.0	Colon array	457-516
DEX0451_033.nt.1	33561	33561.0	Breast array	737-796

DEX0451_033.nt.1	12500	12500.0	Breast array	790-849
DEX0451_033.nt.1	5781	5781.0	Lung array	777-836
DEX0451_033.nt.1	33560	33560.0	Breast array	777-836
DEX0451_033.nt.2	5782	5782.0	Lung array	412-471
DEX0451_033.nt.2	33561	33561.0	Breast array	413-472
DEX0451_033.nt.2	36947	36947.0	Colon array	453-512
DEX0451_033.nt.2	5781	5781.0	Lung array	453-512
DEX0451_033.nt.2	5504	5504.0	Lung array	59-118
DEX0451_033.nt.2	36948	36948.0	Colon array	410-469
DEX0451_033.nt.2	5503	5503.0	Lung array	83-142
DEX0451_033.nt.2	12500	12500.0	Breast array	466-525
DEX0451_033.nt.2	29721	29721.02	Prostate1 array	453-512
DEX0451_033.nt.2	33560	33560.0	Breast array	453-512
DEX0451_033.nt.2	38489	38489.0	Colon array	133-192
DEX0451_034.nt.1	27151	27151.0	Breast array	1116-1175
DEX0451_034.nt.1	14003	14003.0	Breast array	786-845
DEX0451_034.nt.1	27152	27152.0	Breast array	876-935
DEX0451_034.nt.1	14004	14004.0	Breast array	680-739
DEX0451_036.nt.1	35114	35114.0	Colon array	1258-1317
DEX0451_036.nt.1	23859	23859.0	Breast array	1952-2011
DEX0451_036.nt.1	35115	35115.0	Colon array	1103-1162
DEX0451_036.nt.1	37858	37858.0	Breast array	864-923
DEX0451_036.nt.1	23858	23858.0	Breast array	2009-2068
DEX0451_036.nt.2	35115	35115.0	Colon array	3666-3725
DEX0451_036.nt.2	23859	23859.0	Breast array	4515-4574
DEX0451_036.nt.2	23858	23858.0	Breast array	4572-4631
DEX0451_036.nt.2	37858	37858.0	Breast array	3427-3486
DEX0451_036.nt.2	35114	35114.0	Colon array	3821-3880
DEX0451_036.nt.3	37858	37858.0	Breast array	865-924
DEX0451_036.nt.3	23859	23859.0	Breast array	1953-2012
DEX0451_036.nt.3	35115	35115.0	Colon array	1104-1163
DEX0451_036.nt.3	23858	23858.0	Breast array	2010-2069
DEX0451_036.nt.3	35114	35114.0	Colon array	1259-1318
DEX0451_037.nt.1	15066	15066.0	Breast array	216-275
DEX0451_037.nt.1	15045	15045.0	Breast array	443-502
DEX0451_037.nt.2	15063	15063.0	Breast array	896-955
DEX0451_037.nt.2	33432	33432.0	Breast array	714-773
DEX0451_037.nt.2	15045	15045.0	Breast array	581-640
DEX0451_037.nt.2	19356	19356.0	Colon array	719-778
DEX0451_037.nt.2	15044	15044.0	Breast array	624-683
DEX0451_037.nt.2	15062	15062.0	Breast array	928-987
DEX0451_037.nt.2	15066	15066.0	Breast array	354-413
DEX0451_037.nt.3	33432	33432.0	Breast array	644-703
DEX0451_037.nt.3	15045	15045.0	Breast array	511-570
DEX0451_037.nt.3	15066	15066.0	Breast array	284-343
DEX0451_037.nt.3	15044	15044.0	Breast array	554-613
DEX0451_037.nt.3	15063	15063.0	Breast array	826-885
DEX0451_037.nt.3	19356	19356.0	Colon array	649-708
DEX0451_037.nt.3	15062	15062.0	Breast array	858-917
DEX0451_037.nt.4	19356	19356.0	Colon array	1338-1397
DEX0451_037.nt.4	15045	15045.0	Breast array	1200-1259
DEX0451_037.nt.4	15066	15066.0	Breast array	973-1032
DEX0451_037.nt.4	15044	15044.0	Breast array	1243-1302
DEX0451_037.nt.4	33432	33432.0	Breast array	1333-1392
DEX0451_037.nt.4	15071	15071.0	Breast array	1843-1902
DEX0451_037.nt.5	15062	15062.0	Breast array	331-390

DEX0451_037.nt.5	15063	15063.0	Breast array	299-358
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Example 2b: Relative Quantitation of Gene Expression

Real-Time quantitative PCR with fluorescent Taqman® probes is a quantitation detection system utilizing the 5'- 3' nuclease activity of Taq DNA polymerase. The 5 method uses an internal fluorescent oligonucleotide probe (Taqman®) labeled with a 5' reporter dye and a downstream, 3' quencher dye. During PCR, the 5'-3' nuclease activity of Taq DNA polymerase releases the reporter, whose fluorescence can then be detected by the laser detector of the Model 7700 Sequence Detection System (PE Applied Biosystems, Foster City, CA, USA). Amplification of an endogenous control is used to standardize the 10 amount of sample RNA added to the reaction and normalize for Reverse Transcriptase (RT) efficiency. Either cyclophilin, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), ATPase, or 18S ribosomal RNA (rRNA) is used as this endogenous control. To calculate relative quantitation between all the samples studied, the target RNA levels for one sample were used as the basis for comparative results (calibrator). Quantitation 15 relative to the "calibrator" can be obtained using the comparative method (User Bulletin #2: ABI PRISM 7700 Sequence Detection System).

The tissue distribution and the level of the target gene are evaluated for every sample in normal and cancer tissues. Total RNA is extracted from normal tissues, cancer tissues, and from cancers and the corresponding matched adjacent tissues. Subsequently, 20 first strand cDNA is prepared with reverse transcriptase and the polymerase chain reaction is done using primers and Taqman® probes specific to each target gene. The results are analyzed using the ABI PRISM 7700 Sequence Detector. The absolute numbers are relative levels of expression of the target gene in a particular tissue compared to the calibrator tissue.

25 One of ordinary skill can design appropriate primers. The relative levels of expression of the BSNA versus normal tissues and other cancer tissues can then be determined. All the values are compared to the calibrator. Normal RNA samples are commercially available pools, originated by pooling samples of a particular tissue from different individuals.

30 The relative levels of expression of the BSNA in pairs of matched samples may also be determined. A matched pair is formed by mRNA from the cancer sample for a

particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. All the values are compared to the calibrator.

In the analysis of matching samples, the BSNA show a high degree of tissue specificity for the tissue of interest. These results confirm the tissue specificity results obtained with normal pooled samples. Further, the level of mRNA expression in cancer samples and the isogenic normal adjacent tissue from the same individual are compared. This comparison provides an indication of specificity for the cancer state (e.g. higher levels of mRNA expression in the cancer sample compared to the normal adjacent).

- Informaton on the samples tested in the QPCR experiments below include the
- 10 Sample ID (Smpl ID), Tissue, Tissue Type (Tiss Type), Diagnosis (DIAG), Disease Detail, and Stage or Grade (STG or GRD) in following table.

Sample ID	Tissue	Tiss Type	Diagnosis	Disease Detail	Stage or Grade
355	Mammary	CAN	Invasive lobular carcinoma	Invasive lobular carcinoma	Stage IIB
355	Mammary	NAT	NAT		
B011X	Mammary	CAN		Cancer	
B011X	Mammary	NAT		NAT	
S621	Mammary	CAN	Infiltrating ductal carcinoma	Infiltrating Duct Adenocarcinoma	G3; T1NxMx
S621	Mammary	NAT		NAT	
S516	Mammary	CAN	Infiltrating ductal carcinoma	Infiltrating Ductal Carcinoma with Lymphatic Invasion	Stage I G2; T1NoMo
S516	Mammary	NAT		NAT	
522	Mammary	CAN	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma	G III
522	Mammary	NAT		NAT	
76DN	Mammary	CAN		Invasive ductal carcinoma	G3, poorly diff.
76DN	Mammary	NAT		NAT	
19DN	Mammary	CAN	Invasive ductal carcinoma	Invasive ductal carcinoma	G3, Stage IIA; T2N0M0
19DN	Mammary	NAT		NAT	
42DN	Mammary	CAN	Invasive ductal carcinoma	Invasive Ductal Carcinoma	T3aN1M0 IIIA, G3
42DN	Mammary	NAT		NAT	
517	Mammary	CAN	Infiltrating ductal carcinoma	Infiltrating ductal carcinoma	St. IIA, G3
517	Mammary	NAT		NAT	

781M	Mammary	CAN	Invasive ductal carcinoma		Architectural grade-3/3,Nuclear grade-3/3
781M	Mammary	NAT		NAT	
869M	Mammary	CAN	Invasive carcinoma	Invasive Carcinoma	Stage IIA G1;T2NoMo
869M	Mammary	NAT		NAT	
976M	Mammary	CAN	Invasive ductal carcinoma	Invasive Ductal Carcinoma	T2N1M0 (Stage 2B Grade 2-3)
976M	Mammary	NAT		NAT	
S570	Mammary	CAN	Carcinoma	Carcinoma	Stage IIA;T1N1Mo
S570	Mammary	NAT		NAT	
S699	Mammary	CAN	Invasive lobular carcinoma	Invasive Lobular Carcinoma	Stage IIB G1;T2N1Mo
S699	Mammary	NAT		NAT	
S997	Mammary	CAN	Invasive ductal carcinoma	Invasive Ductal Carcinoma	Stage IIB G3; T2N1Mo
S997	Mammary	NAT		NAT	
030B	Urinary Bladder	CAN	Carcinoma	invasive Carcinoma, poorly differentiated	Stage III,Grade 3
030B	Urinary Bladder	NAT		NAT	
520B	Urinary Bladder	CAN	Sarcomatoid transitional cell carcinoma	Sarcomatoid transitional cell carcinoma	
520B	Urinary Bladder	NAT		NAT	
TR17	Urinary Bladder	CAN	Carcinoma	transitional cell carcinoma	Stage II/Grade II
TR17	Urinary Bladder	NAT		NAT	
401C	Colon	CAN	Adenocarcinoma	Adenocarcinoma of ascending colon and cecum	Stage III
401C	Colon	NAT		NAT	
AS43	Colon	CAN	Adenocarcinoma	malignant	
AS43	Colon	NAT	Adenocarcinoma	NAT	
AS98	Colon	CAN	Adenocarcinoma	Moderately to poorly differentiated adenocarcinoma	Duke's C
AS98	Colon	NAT		NAT	
CM12	Colon	CAN		T	Stage D
CM12	Colon	NAT	Adenocarcinoma	Nat	
DC19	Colon	CAN		T	Stage B
DC19	Colon	NAT		NL	
RC01	Colon	CAN	Cancer		Stage IV
RC01	Colon	NAT		NAT	

RS53	Colon	CAN	Adenocarcinoma	moderately differentiated adenocarcinoma	
RS53	Colon	NAT	Adenocarcinoma	NAT	
SG27	Colon	CAN		malig	Stage B
SG27	Colon	NAT		NAT	
TX01				Moderately differentiated adenocarcinoma of cecum	Stage II; T3NoMo
TX01	Colon	CAN	Adenocarcinoma	NAT	
KS52	Cervix	CAN	Squamous cell carcinoma	Keratinizing Squamous Cell Carcinoma	IIIB, well diff. G1; T3bNxM0
KS52	Cervix	NAT		NAT	
NK23	Cervix	CAN		Nonkeratinizing Large Cell	FIGO IIIB, undiff. G4; T3bNxM0
NK23	Cervix	NAT		NAT	
NKS54	Cervix	CAN	Squamous cell carcinoma	Nonkeratinizing Squamous Cell Carcinoma	IIB, mod diff. G2; T2bNxM0
NKS54	Cervix	NAT		NAT	
NKS55	Cervix	CAN	Squamous cell carcinoma	Nonkeratinizing Squamous Cell Carcinoma	IIIB, Mod diff. G2; T3bNxM0
NKS55	Cervix	NAT		NAT	
NKS81	Cervix	CAN	Squamous cell carcinoma	large cell nonkeratinizing sq carc, IIB, moderately diff	IIB
NKS81	Cervix	NAT		NAT	
10479	Endometrium	CAN		malignant mixed mullerian tumor	T?, Nx, M1
10479	Endometrium	NAT		NAT	
28XA	Endometrium	CAN	Endometrial adenocarcinoma	malignant	II/III
28XA	Endometrium	NAT		NAT	II/III
8XA	Endometrium	CAN	mod. diff, invasive, squamous differentiation, FIGO-II		
8XA	Endometrium	NAT		NAT	
106XD	Kidney	CAN	Renal cell carcinoma	renal cell carcinoma, clear cell, localized	
106XD	Kidney	NAT		NL	3

107XD	Kidney	CAN	Renal cell carcinoma	renal cell carcinoma, clear cell, with metastatic	G III
107XD	Kidney	NAT		NL	
109XD	Kidney	CAN		Malignant	G III
109XD	Kidney	NAT		NL	
10XD	Kidney	CAN	Renal cell carcinoma	renal cell carcinoma, clear cell, localized, grade 2-3	3
10XD	Kidney	NAT		NL	
22K	Kidney	CAN	Renal cell carcinoma	Renal cell carcinoma	G2, Mod. Diff.
22K	Kidney	NAT		NAT	
15XA	Liver	CAN		Sarcoma, Retrop eritoneal Tumor	Grade-2
15XA	Liver	NAT		CA	St. I, G4
174L	Liver	CAN	Hepatocellular carcinoma	Moderate to well differentiated hepatocellular carcinoma	
174L	Liver	NAT	Hepatocellular carcinoma	NAT	
187L	Liver	CAN	Adenocarcinoma	Metastatic Adenocarcinoma	Liver (Gallbladder)
187L	Liver	NAT		NAT	
205L	Lung	CAN	Adenocarcinoma	poorly differentiated adenocarcinoma	T2, N1, Mx
205L	Lung	NAT		NAT	
315L	Lung	CAN	Squamous cell carcinoma		
315L	Lung	NAT	Adenocarcinoma	NAT	
507L	Lung	CAN	Bronchioloalveolar carcinoma	bronchioalveolar carcinoma	Stage IB, G1, well diff.
507L	Lung	NAT		NAT	
528L	Lung	CAN	Adenocarcinoma	Adenocarcinoma	St. IV, T2N0M1, infiltrating poorly diff.
528L	Lung	NAT		NAT	
8837L	Lung	CAN	Squamous cell carcinoma	Squamous cell carcinoma	T2, N0, M0
8837L	Lung	NAT		NAT	
AC11	Lung	CAN	Adenocarcinoma	poorly differentiated adenocarcinoma	T2, N2, M1
AC11	Lung	NAT		NAT	
AC39	Lung	CAN	Adenocarcinoma	intermediate grade adenocarcinoma	T2, N2, Mx
AC39	Lung	NAT		NAT	

SQ80	Lung	CAN	Squamous cell carcinoma	poorly differentiated squamous cell carcinoma	T1, N1, M0
SQ80	Lung	NAT		NAT	
SQ81	Lung	CAN	Squamous cell carcinoma	poorly differentiated squamous carcinoma	T3, N1, Mx
SQ81	Lung	NAT		NAT	
G021	Ovary	CAN	Carcinoma	St. IIIC, poorly diff.	Stage- IIIC, poorly diff.
G021	Ovary	NAT		NAT	
206I	Ovary	NRM		NL	
5150	Ovary	NRM		Normal	
18GA	Ovary	NRM		NL	
3370	Ovary	NRM		Normal	
1230	Ovary	NRM		Normal	
C177	Ovary	NRM		several fluid filled cysts	
40G	Ovary	NRM		NL	
10050	Ovary	CAN		papillary serous and endometrioid ovarian carcinoma, concurrent metastatic breast cancer	3
10400	Ovary	CAN		papillary serous adeno, metastatic	
1050	Ovary	CAN		Papillary Serous Carcinoma with Focal Mucinous Differentiation	Stage IC G0; T1cNOMO
130X	Ovary	CAN		Ovarian cancer	
C004	Ovary	NRM		NL	
7180	Ovary	CAN	Adenocarcinoma	malignant tumor	IIIC
A1B	Ovary	CAN	Adenocarcinoma	CA	
71XL	Pancreas	CAN		villous adenoma with paneth cell metaplasia	localized
71XL	Pancreas	NAT		NL	
82XP	Pancreas	CAN		serious cystadenoma	
82XP	Pancreas	NAT		NL	
92X	Pancreas	CAN	Ductal adenocarcinoma	ductal adenocarcinoma	mod to focally poorly diff.
92X	Pancreas	NAT		NL	
23B	Prostate	CAN		Prostate tumor	Gleason's 3+4
23B	Prostate	NAT		NAT	
675P	Prostate	CAN	Adenocarcinoma	adenocarcinoma	
675P	Prostate	NAT		Normal	
958P	Prostate	CAN	Adenocarcinoma	Adenocarcinoma	T2C, NO, MX

958P	Prostate	NAT		NAT	
65XB	Prostate	CAN	Adenocarcinoma	adenocarcinom	3+4=7
65XB	Prostate	NAT		NL	
84XB	Prostate	CAN	Adenocarcinoma	adenocarcinom	2+3
84XB	Prostate	NAT		NL	
855P	Prostate	BPH		BPH	
276P	Prostate	BPH		BPH	
767B	Prostate	BPH		prostate BPH	
263C	Prostate	BPH		BPH	
10R	Prostate	PROS T		active chronic prostatitis	T0, NO, MO
20R	Prostate	PROS T		PROSTATITIS	
39A	Skin	CAN		CA	St. II
39A	Skin	NAT		CA	St. II
287S	Skin	CAN	Squamous cell carcinoma	Invasive Keratinizing Squamous Cell Carcinoma	Moderately Differentiated
287S	Skin	NAT		NAT	
669S	Skin	CAN	Melanoma	Nodular malignant melanoma	
669S	Skin	NAT		NAT	
171S	Small Intestin e	CAN	Adenocarcinoma	Moderately differentiated Adenocarcinoma , invasive	
171S	Small Intestin e	NAT		NAT	
H89	Small Intestin e	CAN	Adenocarcinoma	Adenocarcimoa	80% tumor, 50% necrosis, moderately differentiated , G2-3; T3N1MX
H89	Small Intestin e	NAT	Adenocarcinoma	NAT	
20SM	Small Intestin e	CAN	Adenocarcinoma	Adenocarcinoma , metastatic to lung & liver	St. IV, poorly diff.
20SM	Small Intestin e	NAT		NAT	
88S	Stomach	CAN	Adenocarcinoma	Mucinous adenocarcinoma	T3N1M0, St. IIIA
88S	Stomach	NAT		NAT	
261S	Stomach	CAN	Signet-ring cell carcinoma	Signet-ring cell carcinoma	Stage IIIA, T3N1M0
261S	Stomach	NAT		NAT	
288S	Stomach	CAN	Adenocarcinoma	Infiltrating Adneocarcinoma	Moderately Differentiated
288S	Stomach	NAT		NAT	
AC93 or 509L	Stomach	CAN	Adenocarcinoma	Adenocarcinoma	St. IV, G4, T4N3M0, poorly diff.

AC93 or 509L				NAT	
39X	Stomach	NAT		CA	
39X	Testes	CAN		NAT	
647T	Testes	CAN	Teratocarcinoma	Teratocarcinoma	Stage IA
647T	Testes	NAT	Teratocarcinoma	NAT	
663T	Testes	CAN	Teratocarcinoma	Teratocarcinoma	
663T	Testes	NAT		NAT	
56T	Thyroid Gland	CAN	Papillary carcinoma	Papillary Carcinoma	St. III; T4N1M0
56T	Thyroid Gland	NAT		NAT	
143N	Thyroid Gland	CAN	Follicular carcinoma	Follicular Carcinoma	
143N	Thyroid Gland	NAT		NAT	
270T	Thyroid Gland	CAN		CA	
270T	Thyroid Gland	NAT		NAT	
135XO	Uterus	CAN		Uterus normal	
135XO	Uterus	NAT		Uterus tumor	
85XU	Uterus	CAN		endometrial carcinoma	I
85XU	Uterus	NAT		NL	
B1	Blood	NRM		Normal	
B3	Blood	NRM		Normal	
B5	Blood	NRM		Normal	
B6	Blood	NRM		Normal	
B11	Blood	NRM		Normal	
982B	Blood	NRM		Normal	
48AD	Adrenal Gland	NRM		Normal	
10BR	Brain	NRM		Normal	
01CL	Colon	NRM		Normal	
06CV	Cervix	NRM		Normal	
01ES	Esophagus	NRM		Normal	
46HR	Heart	NRM		Normal	
00HR	Human Reference	CAN	CAN	Cancer pool	
55KD	Kidney	NRM		Normal	
89LV	Liver	NRM		Normal	
90LN	Lung	NRM		Normal	
01MA	Mammary	NRM		Normal	
84MU	Skeletal Muscle	NRM		Normal	
3APV	Ovary	NRM		Normal	
04PA	Pancreas	NRM		Normal	
59PL	Placenta	NRM		Normal	
09PR	Prostate	NRM		Normal	
21RC	Rectum	NRM		Normal	

59SM	Small Intestine	NRM		Normal	
7GSP	Spleen	NRM		Normal	
09ST	Stomach	NRM		Normal	
4GTS	Testes	NRM		Normal	
99TM	Thymus Gland	NRM		Normal	
16TR	Trachea	NRM		Normal	
57UT	Uterus	NRM		Normal	

DEX0451_015.nt.1 (Mam126)

The relative expression level of Mam126 in various tissue samples is included below. Tissue samples include 76 pairs of matching samples, 7 non matched cancer samples, and 34 normal samples, all from various tissues annotated in the table. A matching pair is formed by mRNA from the cancer sample for a particular tissue and mRNA from the normal adjacent sample for that same tissue from the same individual. Of the normal samples 5 were blood samples which measured the expression levels in blood cells. Additionally, 2 prostatitis (PROST), and 4 Benign Prostatic Hyperplasia (BPH) samples are included. All the values are compared to breast cancer sample MAM522 (calibrator).

The table below contains the relative expression level values for the sample as compared to the calibrator. The table includes the Tissue Abbreviation and Sample ID (Tiss Abrev, Sample ID), and expression level values for the following samples: Cancer (CAN), Normal Adjacent Tissue (NAT), Normal Tissue (NRM), Benign Prostatic Hyperplasia (BPH), and Prostatitis (PROST).

Tiss Abbrev, Sample ID	CAN	NAT	NRM	BPH	PROST
MAM355	3.81	0.02			
MAMB011X	0.08	0.47			
MAMS621	1.11	0.51			
MAMS516	0.00	2.92			
MAM522	1.00	0.07			
MAM76DN	0.43	0.40			
MAM976M	0.34	0.00			
MAM781M	1.17	0.00			
MAM19DN	0.29	0.50			
MAM517	1.43	0.00			
MAMS997	2.58	0.33			
MAM869M	0.01				
MAMS699	0.00	0.00			

MAMS570	0.00	0.69			
BLD030B	0.00	0.29			
BLD520B	1.27	0.43			
BLDTR17	0.67	0.17			
CLN401C	0.05	0.02			
CLNAS43	0.10	0.00			
CLNAS98	0.10	0.00			
CLNCM12	0.16	0.03			
CLNDC19	0.00	0.00			
CLNRC01	0.06	0.01			
CLNRS53	0.52	0.25			
CLNSG27	0.19	0.00			
CLNTX01	0.11	0.00			
CVXKS52	0.00	0.04			
CVXNK23	0.02	0.00			
CVXNKS54	0.64	0.28			
CVXNKS55	0.00	0.07			
CVXNKS81	0.11	0.00			
ENDO10479	0.20	0.00			
ENDO28XA	0.11	0.10			
ENDO8XA	0.88	0.06			
KID106XD	0.00	0.04			
KID107XD	0.00	0.05			
KID109XD	0.03	0.00			
KID10XD	0.00	0.03			
KID22K	0.02	0.05			
LNG205L	0.18	0.00			
LNG315L	0.04	0.00			
LNG507L	0.37	0.00			
LNG528L	0.08	0.12			
LNG8837L	0.08	0.40			
LNGAC11	0.71	0.18			
LNGAC39	0.18	0.33			
LNGSQ80	0.13	0.30			
LNGSQ81	0.78	0.28			
LVR15XA	0.03	0.06			
LVR174L	0.17	0.07			
LVR187L	0.00	0.00			
OVRG021	0.14	0.28			
OVR10050	0.73				
OVR10400	2.20				
OVR1050	0.09				
OVR130X	0.00				
OVRA1B	0.42				
OVR1230		0.58			
OVR18GA		2.21			
OVR206I		1.70			

OVR337O			0.00		
OVR40G			1.00		
OVR515O			0.26		
OVRC004			0.00		
OVRC177			0.75		
PAN71XL	0.03	0.07			
PAN82XP	0.02	0.00			
PAN92X	0.18	0.00			
PRO23B	0.10	0.05			
PRO65XB	0.61	1.73			
PRO675P	0.26	0.41			
PRO84XB	2.44	0.14			
PRO958P	0.14	0.05			
PRO263C			0.00		
PRO276P			0.02		
PRO767B			0.07		
PRO855P			0.02		
PRO10R				0.00	
PRO20R				0.00	
SKN287S	0.15	0.21			
SKN39A	0.58	0.69			
SKN669S	2.47	0.18			
SMINT171S	0.00	0.00			
SMINT20SM	0.23	0.08			
SMINTH89	0.35	0.09			
STO261S	0.00	0.00			
STO288S	0.17	0.03			
STO88S	0.00	0.03			
THRD143N	0.41	0.17			
THRD270T	0.03	0.00			
THRD56T	0.25	0.00			
TST39X	0.97	0.37			
TST647T	3.18	0.23			
TST663T	6.63	0.20			
UTR135XO	0.16	0.20			
UTR85XU	0.56	1.22			
BLOB1			0.00		
BLOB3			0.00		
BLOB6			0.00		
BLOB11			0.00		
BLO982B			0.00		
ADR48AD			0.19		
CLN01CL			0.00		
ESO01ES			0.00		
HRT46HR			0.03		
HUMREF00HR	1.50				
KID55KD			0.05		

LVR89LV		0.07		
LNG90LN		1.14		
MAM01MA		2.19		
MSL84MU		0.00		
OVR3APV		2.36		
PAN04PA		0.00		
PLA59PL		1.02		
PRO09PR		0.17		
REC21RC		0.08		
SMINT59SM		0.01		
SPL7GSP		0.29		
STO09ST		0.00		
THYM99TM		0.00		
TRA16TR		0.56		
TST4GTS		0.01		
UTR57UT		0.07		

0.00= Negative or no expression

The sensitivity for Mam126 expression was calculated for the cancer samples versus normal samples. The sensitivity value indicates the percentage of cancer samples
5 that show levels of Mam126 at least 2 fold higher than the normal tissue or the corresponding normal adjacent form the same patient.

This specificity is an indication of the level of breast tissue specific expression of the transcript compared to all the other tissue types tested in our assay. Thus, these experiments indicate Mam126 being useful as a breast cancer diagnostic marker and/or
10 therapeutic target.

Sensitivity and specificity data is reported in the table below.

	CLN	LNG	MAM	OVR	PRO
Sensitivity, Up vs. NAT	89%	56%	50%	0%	40%
Sensitivity, Down vs. NAT	0%	22%	21%	0%	20%
Sensitivity, Up vs. NRM	89%	0%	0%	17%	40%
Sensitivity, Down vs. NRM	0%	78%	60%	50%	0%
Specificity	27.32 %	31.15 %	39.53 %	37.1 %	34.59 %

Altogether, the tissue specificity, plus the mRNA differential expression in the samples tested are believed to make Mam126 a good marker for diagnosing, monitoring,
15 staging, imaging and/or treating breast cancer.

Additionally, the tissue specificity, plus the mRNA differential expression in the samples tested are believed to make Mam126 a good marker for diagnosing, monitoring, staging, imaging and/or treating colon cancer.

Primers used for QPCR Expression Analysis of Mam126 are as follows:

- 5 (Mam126_forward): CTTGTGACAGCCACGACTTTG (SEQ ID NO:180)
 (Mam126_reverse): GCATCCAGCCAGGCTTCTC (SEQ ID NO:181)
 (Mam126_probe): TTTGTTGTTAATGTAATTAGAGACACCAG (SEQ ID NO:182)

Conclusions

10 Altogether, the high level of tissue specificity, plus the mRNA overexpression in matched samples tested are indicative of SEQ ID NO: 1-72 being a diagnostic marker and/or a therapeutic target for cancer.

Example 3: Protein Expression

The BSNA is amplified by polymerase chain reaction (PCR) and the amplified DNA fragment encoding the BSNA is subcloned in pET-21d for expression in E. coli. In addition to the BSNA coding sequence, codons for two amino acids, Met-Ala, flanking the NH₂-terminus of the coding sequence of BSNA, and six histidines, flanking the COOH-terminus of the coding sequence of BSNA, are incorporated to serve as initiating Met/restriction site and purification tag, respectively.

20 An over-expressed protein band of the appropriate molecular weight may be observed on a Coomassie blue stained polyacrylamide gel. This protein band is confirmed by Western blot analysis using monoclonal antibody against 6X Histidine tag.

Large-scale purification of BSP is achieved using cell paste generated from 6-liter bacterial cultures, and purified using immobilized metal affinity chromatography (IMAC).
25 Soluble fractions that are separated from total cell lysate were incubated with a nickel chelating resin. The column is packed and washed with five column volumes of wash buffer. BSP is eluted stepwise with various concentration imidazole buffers.

Example 4: Fusion Proteins

The human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5'and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector. For example, if pC4 (Accession No.

209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 2, is ligated into this 5 BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced. If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. See, e.g., WO 96/34891.

10 **Example 5: Production of an Antibody from a Polypeptide**

In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100, µg/ml of streptomycin. The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP20), available from 15 the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands *et al.*, *Gastroenterology* 80: 225-232 (1981).

The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide. Alternatively, 20 additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such 25 an animal are then used to produce hybridoma cells; and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic 30

antibodies to the protein specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

Example 6: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

5 RNA is isolated from individual patients or from a family of individuals that have a phenotype of interest. cDNA is then generated from these RNA samples using protocols known in the art. See, Sambrook (2001), *supra*. The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO: 1-72. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; 10 and 60-120 seconds at 70°C, using buffer solutions described in Sidransky *et al.*, *Science* 252(5006): 706-9 (1991). See also Sidransky *et al.*, *Science* 278(5340): 1054-9 (1997).

15 PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTTM Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons are also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing. PCR products are cloned into T-tailed vectors as described in Holton *et al.*, *Nucleic Acids Res.*, 19: 1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

20 Genomic rearrangements may also be determined. Genomic clones are nick-translated with digoxigenin deoxyuridine 5' triphosphate (Boehringer Manheim), and FISH is performed as described in Johnson *et al.*, *Methods Cell Biol.* 35: 73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

25 Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C-and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. Johnson (1991). Image collection, analysis and 30 chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the

genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 7: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

5 Antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described above. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced. The coated wells are then
10 incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide. Next, 50 µl of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three
15 times with deionized or distilled water to remove unbound conjugate. 75 µl of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution are added to each well and incubated 1 hour at room temperature.

The reaction is measured by a microtiter plate reader. A standard curve is prepared, using serial dilutions of a control sample, and polypeptide concentrations are
20 plotted on the X-axis (log scale) and fluorescence or absorbance on the Y-axis (linear scale). The concentration of the polypeptide in the sample is calculated using the standard curve.

Example 8: Formulating a Polypeptide

The secreted polypeptide composition will be formulated and dosed in a fashion
25 consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

30 As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1, µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to

therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 μ g/kg/hour to about 50 mg/kg/hour, either by 1-4 injections per day or by continuous 5 subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are 10 administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which 15 include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained- 20 release matrices include polylactides (U. S. Pat. No.3,773,919, EP 58,481, the contents of which are hereby incorporated by reference herein in their entirety), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22: 547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15: 167-277 (1981), and R. Langer, Chem. Tech. 12: 98-105 (1982)), ethylene vinyl acetate 25 (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE Epstein et al., Proc. Natl. Acad. Sci. USA 82: 3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese 30 Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324, the contents of which are hereby incorporated by reference herein in their entirety. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the

lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage

- 5 injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation.

For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides. Generally, the

- 10 formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably, the carrier is a parenteral carrier, more preferably, a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-
15 aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

- The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate,
20 succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e. g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates
25 including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

- The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will
30 be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron

membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for
5 example, sealed ampules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1 % (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

10 The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container (s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or
15 sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

Example 9: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by
20 administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

25 For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided above.

Example 10: Method of Treating Increased Levels of the Polypeptide

30 Antisense or RNAi technology are used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided
5 above.

Example 11: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and
10 separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e. g., Ham's F12 media, with 10% FBS, penicillin and
15 streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks. pMV-7 (Kirschmeier, P. T. et al.,
DNA, 7: 219-25 (1988)), flanked by the long terminal repeats of the Moloney murine
20 sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5'and 3'end sequences respectively as set forth in
25 Example 3. Preferably, the 5'primer contains an EcoRI site and the 3'primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB 101, which are
30 then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now 5 produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached 10 producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media.

If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector 15 that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 12: Method of Treatment Using Gene Therapy-In Vivo

20 Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide.

The polynucleotide of the present invention may be operatively linked to a 25 promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, Tabata H. *et al.* *Cardiovasc. Res.* 35 (3): 470-479 (1997); Chao J *et al.* *Pharmacol. Res.* 35 (6): 517-522 (1997); Wolff J. A. *Neuromuscul. Disord.* 7 (5): 314-318 (1997), Schwartz B. *et al.* *Gene Ther.* 3 (5): 405-411 (1996); and Tsurumi Y. *et* 30 *al.* *Circulation* 94 (12): 3281-3290 (1996); WO 90/11092, WO 98/11779; U. S. Patent No. 5,693,622; 5,705,151; 5,580,859, the contents of which are hereby incorporated by reference herein in their entirety.

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, breast, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

5 The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P. L. *et al. Ann. NY Acad. Sci.* 772: 126-139 (1995) and Abdallah B. *et al. Biol. Cell.* 85 (1): 1-7 (1995)) which 10 can be prepared by methods well known to those skilled in the art.

10 The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art 15 can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

20 The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, breast, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide 25 matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They 30 may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin

fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 µg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to breasts or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle in vivo is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection

may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice.

The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

5 **Example 13: Transgenic Animals**

The polypeptides of the invention can also be expressed in transgenic animals.

Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e. g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (I. e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection

15 (Paterson et al., *Appl. Microbiol. Biotechnol.* 40: 691-698 (1994); Carver et al., *Biotechnology* 11: 1263-1270 (1993); Wright et al., *Biotechnology* 9: 830-834 (1991); and U. S. Pat. No. 4,873,191, the contents of which is hereby incorporated by reference herein in its entirety); retrovirus mediated gene transfer into germ lines (Van der Putten et al., *Proc. Natl. Acad. Sci., USA* 82: 6148-6152 (1985)), blastocysts or embryos; gene targeting
20 in embryonic stem cells (Thompson et al., *Cell* 56: 313-321 (1989)); electroporation of cells or embryos (Lo, 1983, *Mol Cell. Biol.* 3: 1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e. g., Ulmer et al., *Science* 259: 1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm mediated gene transfer
25 (Lavitrano et al., *Cell* 57: 717-723 (1989). For a review of such techniques, see Gordon, "Transgenic Animals," *Intl. Rev. Cytol.* 115: 171-229 (1989).

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence

30 (Campell et al., *Nature* 380: 64-66 (1996); Wilmut et al., *Nature* 385: 810813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells,

I. e., mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, e.g., head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., 5 *Proc. Natl. Acad. Sci. USA* 89: 6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some 10 nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et 15 al. (Gu et al., *Science* 265: 103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished 20 by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). 25 Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding 30 strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous

transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 14: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (E. g., see Smithies et al., *Nature* 317: 230-234 (1985); Thomas & Capecchi, *Cell* 51: 503512 (1987); Thompson et al., *Cell* 5: 313-321 (1989)) Alternatively, RNAi technology may be used. For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfet cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e. g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However, this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e. g., knockouts) are administered to a

patient in vivo. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e. g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered in vitro using recombinant DNA techniques

5 to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs,

10 naked DNA, electroporation, liposomes, etc.

The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be

15 introduced into the patient systemically, e. g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e. g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U. S. Patent No. 5,399,349; and

20 Mulligan & Wilson, U. S. Patent No. 5,460,959, the contents of which are hereby incorporated by reference herein in their entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the

25 cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of

30 polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

210

While preferred illustrative embodiments of the present invention are described, one skilled in the art will appreciate that the present invention can be practiced by other than the described embodiments, which are presented for purposes of illustration only and not by way of limitation. The present invention is limited only by the claims that follow.

5

We claim:

1. An isolated nucleic acid molecule comprising:
 - (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 73-179;
 - 5 (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-72;
 - (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or
 - (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b).
- 10 2. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a cDNA.
- 15 3. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is genomic DNA.
4. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is an RNA.
- 20 5. The nucleic acid molecule according to claim 1, wherein the nucleic acid molecule is a mammalian nucleic acid molecule.
- 25 6. The nucleic acid molecule according to claim 5, wherein the nucleic acid molecule is a human nucleic acid molecule.
7. A method for determining the presence of a breast specific nucleic acid (BSNA) in a sample, comprising the steps of:
 - (a) contacting the sample with the nucleic acid molecule of SEQ ID NO: 1-72 under conditions in which the nucleic acid molecule will selectively hybridize to a breast specific nucleic acid; and

- (b) detecting hybridization of the nucleic acid molecule to a BSNA in the sample, wherein the detection of the hybridization indicates the presence of a BSNA in the sample.
- 5 8. A vector comprising the nucleic acid molecule of claim 1.
9. A host cell comprising the vector according to claim 8.
10. A method for producing a polypeptide encoded by the nucleic acid molecule
10 according to claim 1, comprising the steps of:
- (a) providing a host cell comprising the nucleic acid molecule operably linked to one or more expression control sequences, and
- (b) incubating the host cell under conditions in which the polypeptide is produced.
- 15
11. A polypeptide encoded by the nucleic acid molecule according to claim 1.
12. An isolated polypeptide selected from the group consisting of:
- (a) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 73-179 ; or
- 20 (b) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-72.
- 25 13. An antibody or fragment thereof that specifically binds to:
- (a) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 73-179 ; or
- (b) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule
30 comprising a nucleic acid sequence of SEQ ID NO: 1-72.
14. A method for determining the presence of a breast specific protein in a sample, comprising the steps of:

- (a) contacting the sample with a suitable reagent under conditions in which the reagent will selectively interact with the breast specific protein comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 73-179; and
- 5 (b) detecting the interaction of the reagent with a breast specific protein in the sample, wherein the detection of binding indicates the presence of a breast specific protein in the sample.
15. A method for diagnosing or monitoring the presence and metastases of breast cancer in a patient, comprising the steps of:
- 10 (a) determining an amount of:
- (i) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 73-179;
- (ii) a nucleic acid molecule comprising a nucleic acid sequence of SEQ 15 ID NO: 1-72;
- (iii) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (i) or (ii);
- (iv) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (i) or (ii);
- 20 (v) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 73-179 ; or
- (vi) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-72
- 25 and;
- (b) comparing the amount of the determined nucleic acid molecule or the polypeptide in the sample of the patient to the amount of the breast specific marker in a normal control; wherein a difference in the amount of the nucleic acid molecule or the polypeptide in the sample compared to the amount of the nucleic acid molecule or the polypeptide in the normal control is associated with the 30 presence of breast cancer.

16. A kit for detecting a risk of cancer or presence of cancer in a patient, said kit comprising a means for determining the presence of:

- (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 73-179;
- 5 (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-72;
- (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b); or
- 10 (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b); or
- (e) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 73-179 ; or
- 15 (f) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-72.

17. A method of treating a patient with breast cancer, comprising the step of administering a composition consisting of:

- (a) a nucleic acid molecule comprising a nucleic acid sequence that encodes an amino acid sequence of SEQ ID NO: 73-179;
- 20 (b) a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-72;
- (c) a nucleic acid molecule that selectively hybridizes to the nucleic acid molecule of (a) or (b);
- 25 (d) a nucleic acid molecule having at least 95% sequence identity to the nucleic acid molecule of (a) or (b);
- (e) a polypeptide comprising an amino acid sequence with at least 95% sequence identity to of SEQ ID NO: 73-179 ; or
- 30 (f) a polypeptide comprising an amino acid sequence encoded by a nucleic acid molecule having at least 95% sequence identity to a nucleic acid molecule comprising a nucleic acid sequence of SEQ ID NO: 1-72;

to a patient in need thereof, wherein said administration induces an immune response against the breast cancer cell expressing the nucleic acid molecule or polypeptide.

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18. A vaccine comprising the polypeptide or the nucleic acid encoding the polypeptide of claim 12.

5

1

SEQUENCE LISTING

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Macina, Roberto
Turner, Leah
Sun, Yongming

<120> Compositions, Splice Variants and Methods Relating to Breast Specific Genes and Proteins

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<210> 15
<211> 1433
<212> DNA
<213> Homo sapien

<400> 15

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<211> 1937
<212> DNA
<213> Homo sapien

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10

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 <211> 1262
 <212> DNA
 <213> Homo sapien

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 <213> Homo sapien

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12

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<211> 604
<212> DNA
<213> Homo sapien

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13

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<211> 940
<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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<212> DNA
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<211> 1961
 <212> DNA
 <213> Homo sapien

 <400> 31

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<212> DNA
<213> Homo sapien

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 <212> DNA
 <213> Homo sapien

<400> 33

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29

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<211> 2787
<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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<211> 893
<212> DNA
<213> Homo sapien

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32

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<210> 37
<211> 3828
<212> DNA
<213> Homo sapien

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36

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<213> Homo sapien
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<212> DNA
<213> Homo sapien

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 <211> 985
 <212> DNA
 <213> Homo sapien

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 <211> 1815
 <212> DNA
 <213> Homo sapien

<400> 51
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<210> 52
<211> 1298
<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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 <211> 630
 <212> DNA
 <213> Homo sapien

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<210> 55
<211> 714
<212> DNA
<213> Homo sapien

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<210> 56
<211> 950
<212> DNA
<213> Homo sapien

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54

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<211> 280	
<212> DNA	
<213> Homo sapien	
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<211> 294	
<212> DNA	
<213> Homo sapien	
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<213> Homo sapien	
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55

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<212> DNA
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<211> 1042
<212> DNA
<213> Homo sapien

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57

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<213> Homo sapien

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<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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 <213> Homo sapien

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gaccaggggcc ctgggcctcc ccacactccc catggagaag ctggcggcct ctacagagcc	180
ccaaaggccct cggccgggtcc tgggcccgtga gagtgccag gtgcccgtatg accaagactt	240

tgcagcttc	cggtcagagt	gtgaggctga	ggtgggctgg	aacctgaccc	atagcagggc	300
tgggtgtct	gtctgggtgc	aggctgtgga	gatggatcg	acgctgcaca	agatcaagt	360
ccggatggag	tgctgtgatg	tgccagccga	gacactctac	gacgtcctac	acgacattga	420
gtaccgcaag	aatgggaca	gcaacgtcat	tgagactttt	gacatcgccc	gcttgacagt	480
caacgctgac	gtgggctatt	actcctggag	tgtcccaagc	ycctgcgaac	ctatgaggta	540
ccgagctcga	ttcgatcatg	tcaa				564

<210> 69
<211> 1333
<212> DNA
<213> Homo sapien

<400> 69	gcagcctgga	aaatccccag	ccgcggccgc	cgagcccccg	agccccccgag	cccccagcct	60
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	tcctccacc	agagcccccg	cgoggccccg	ggtctcccg	gcagctgagg	cgcgccgcgt	180
	ggcaccccg	ccccggcggg	ccccggcgga	gcggcgggca	aaggctccag	gaaggtggcg	240
	tcagcatctg	cagccgcgtc	gacgttgtcg	gagcctcccc	acactcccc	tggagaagct	300
	ggccgcctct	acagagcccc	aagggcctcg	gccggcctcg	ggccgtgaga	gtgtccaggt	360
	gcccgtgac	caagactttc	gcagcttccg	gtcagagtgt	gaggctgagg	tggctggaa	420
	cctgacccat	agcagggctg	gggtgtctgt	ctgggtgcag	gctgtggaga	tggatcggac	480
	gctgcacaag	atcaagtgcc	ggatggagtg	ctgtgatgtg	ccagccgaga	cactctacga	540
	cgtcctacac	gacattgagt	accgcaagaa	atgggacagc	aacgtcattg	agactttga	600
	catcgccccgc	ttgacagtca	acgctgacgt	ggcttattac	tcctggaggt	gtcccaagcc	660
	cctgaagaac	cgtgatgtca	tcaccctccg	ctcctggctc	cccatgggcg	ctgattacat	720
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	tgtgtccatc	cagacgggct	acctcatcca	gagcacaggg	cccaagagct	gcgtcatcac	840
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	tcagttcctg	gctcccaagg	ccatgaagaa	gatgtacaag	gcgtgcctca	agtacccgaa	960
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	cgagagcgcg	gtggccgaga	gcagagagga	gcggatgggc	ggcgcgccgc	gcgagggcag	1140
	cgacgacgac	acctcgctca	cctgagcgcc	gcacccgttc	agggacggag	acaggaccgg	1200
	gcgagccctg	gggcggcgcc	cgctcctgca	cttctcccc	tccccccaccc	ggcacctgg	1260

ggcacccggc caggcccagg cgggtgctgc agcctggctg gacagagccc caataaacga	1320
tccccacagcc tca	1333

<210> 70
 <211> 1263
 <212> DNA
 <213> Homo sapien

<400> 70	
gccttgtgc ctgcacaac ctgtgaattt gctccatcaa aactggcagg cagggttacc	60
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gatcaaggca gccatoatct gtcgaactag atggtcccag gaaggtggcg tcagcatctg	180
cagccgcgtc gacgttgcg gaggctcccc acactcccc tggagaagct ggccgcctct	240
acagagcccc aagggcctcg gcgggtcctg ggccgtgaga gtgtccaggt gcccgtatgc	300
caagactttc gcagcttccg gtcagagtgt gaggctgagg tggctggaa cctgacatat	360
agcagggctg gggtgtctgt ctgggtgcag gctgtggaga tggatcgac gctgcacaag	420
atcaagtgcc gnatggagtgc ctgtgatgtg ccagccgaga cactctacga cgtcctacac	480
gacattgagt accgcaagaa atggacacgc aacgtcattt agacttttga catcgccgc	540
ttgacagtca acgctgacgt gggctattac tcctggaggt gtcccaagcc cctgaagaac	600
cgtgatgtca tcaccctccg ctccctggctc cccatggcg ctgattacat cattatgaac	660
tactcagtca aacatcccaa atacccacct cgaaaagact tggtccgagc tgtgtccatc	720
cagacgggct acctcatcca gagcacaggg cccaaagagct gcgtcatcac ctacctggcc	780
caggtggacc ccaaaggctc cttacccaag tgggtggta ataaatcttc tcagttcctg	840
gctcccaagg ccatgaagaa gatgtacaag gctgtccatca agtacccoga gtggaaacag	900
aagcacctgc ctcacttcaa ggcgtggctg caccggagc agagcccggt gccgagccgt	960
gcgcgtgcgg agctgtcggt gcagcatgcg gactcactgg agaacatcga cgagagcg	1020
gtggccgaga gcagagagga gggatgggc ggccggggcg gcgaggccag cgacgacgac	1080
acctcgctca cctgagcgcc gcaccgcttc agggacggag acaggaccgg gcgagccctg	1140
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tca	1263

<210> 71
 <211> 1932
 <212> DNA
 <213> Homo sapien

<400> 71	
ctgagcgaag ataaccgtaa taaatagtaa cctaacggtc cagtcatcg tctgtggtcc	60
tttcttttat gattcacaag gaatgaccct cttcatcgcc ttcctaatt cagtcctcac	120
aacagtcctt ttacaaatgg gacaacaggt tagaggaagt caggcagatt tccagcatca	180
tagagagtaa aggaccaggg aaggatcagg attcaaggac tgcacccagg ctctgctcc	240
agcttgctgt gtgactttgg gtaattttgt tcccttaggg aactgagctt tctcatttgt	300
aaatgcaaac aggctgttgg gaggatcaaa tgagatccag gggtaaaaac agcttagttt	360
actttcagga atttacccac gcggtatata aaggcaaaat attattatag tcaggtgatt	420
gtagattgag gaaccttattt ctcattctg caaatgcaa acctgagggc ccaaagaggg	480
acaggggctt gccccaggtc tcagcaggct gtgagcaaga gctaaagcct aatcctcctg	540
cctttgggcc tggagccctt cttgtaccc caggggtcag tgtcttgtt ggatacaggc	600
ttagattgac tgactgtacc ctgagaacct aggggagtcc ctgttcccaa ttcttctcct	660
accccccacct tggcctgatg gaggaagacc ctgctgtt gagatgagca ccagagccaa	720
gaagctgagg aggatctgga gaattctgga ggaagaggag agtgttgctg gagctgtaca	780
gaccctgctt ctcaggtccc aggaagggtgg cgtcagcatc tgcagccgcg tcgacgttgt	840
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cactccccat ggagaagctg gcggccctcta cagagcccca agggcctcgg cggcctcctgg	960
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ctgtggagat ggatcggacg ctgcacaaga tcaagtcccg gatggagtgc tgtgtgtgc	1140
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cgaaggggac actgtgtccc tgcagtgcac ctacagggaa gagctgaggg accacccgaa	1680
gtactggtgc aggaaggggtg ggatccttctt ctctcgctgc tctggcacca tctatggcga	1740
agaagaaggc caggagacaa tgaagggcag ggtgtccatc cgtgacagcc gccaggagct	1800

ctcgctaatt gtgaccctgt ggaacctcac cctgcaagac gctggggagt actggtgtgg 1860
ggtcgaaaaaa cggggcccccgg atgagtcttt actgatctct ctgctcgtct ctccacaccc 1920
tccctgggctc ta 1932

<210> 72
<211> 736
<212> DNA
<213> Homo sapien

<400> 72
tccagccttg ggcaataatg agctactccc agcctgggca ataatgagct actccttagct 60
cggggcaatg aatgagctac taccagctt gggccgataa gagctactcc tagcctgggc 120
aataagagct actccagcct gggcaataag agctactcca gcctggcaa taagagctac 180
tccagcctgg gcaataagag ctactccagc ctgggcaata aggccaaaga gctgcgtcat 240
cacctacctg gcccagggtgg accccaaagg ctccttaccc aagtgggtgg tgaataaattc 300
ttctcagttc ctggctccca aggccatgaa gaagatgtac aaggcgtgcc tcaagtaccc 360
cgagtggaaa cagaagcacc tgccctactt caagccgtgg ctgcacccgg agcagagccc 420
gttgcgcagc ctggcgctgt cggagctgtc ggtgcagcat gcggactcac tggagaacat 480
cgacgagagc gcggtgtggccg agagcagaga ggagcggatg ggccggccgg gcggcgaggg 540
cagcgacgac gacacctcgc tcacctgagc gccgcaccgc ttcaaggacg gagacaggac 600
cgggcgagcc ctggggcgcc ggccgcgtctt gcaactttctc ccctccccca cccggcacct 660
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cgatccccaca gcctca 736

<210> 73
<211> 91
<212> PRT
<213> Homo sapien

<400> 73

Met Cys Gln Pro Val Ser Ile Ser Glu Lys Ala Met Tyr Pro Asp Tyr
1 5 10 15

Phe Ala Lys Arg Glu Gln Trp Lys Lys Leu Arg Arg Glu Ser Trp Glu
 20 25 30

Arg Glu Val Lys Gln Leu Gln Glu Glu Thr Pro Pro Gly Gly Pro Leu
35 40 45

Thr Glu Ala Leu Pro Pro Ala Arg Lys Glu Gly Asp Leu Pro Pro Leu

69

50

55

60

Val Val Val Tyr Cys Asp Gln Thr Pro Gly ser Gly Pro Cys Arg Lys
65 70 75 80

Arg Glu Thr His Leu Ser Cys Leu Gln Val Lys
85 90

<210> 74
<211> 117
<212> PRT
<213> Homo sapien

<400> 74

His Gly Gly Leu His Arg Arg Trp Leu Ser Leu Gly Thr Trp Pro Arg
1 5 10 15

Val Asp Asn Thr Trp Gly Pro Leu Pro Asn Leu Pro Val Pro Gly Gly
20 25 30

Ser His Pro Val Pro Pro Ala Arg Met Cys Gln Pro Val Ser Ile Ser
35 40 45

Glu Lys Ala Met Tyr Pro Asp Tyr Phe Ala Lys Arg Glu Gln Trp Lys
50 55 60

Lys Leu Arg Arg Glu Ser Trp Glu Arg Glu Val Lys Gln Leu Gln Glu
65 70 75 80

Glu Thr Pro Pro Gly Gly Pro Leu Thr Glu Ala Leu Pro Pro Ala Arg
85 90 95

Lys Glu Gly Asp Leu Pro Pro Leu Val Val Val Tyr Cys Asp Gln Thr
100 105 110

Pro Gly Ala Ala Met
115

<210> 75
<211> 157
<212> PRT
<213> Homo sapien

<400> 75

Met Trp Thr Arg Lys Ala Gly Arg Leu Arg Leu Gly Ser Arg Pro Ala
1 5 10 15

70

Pro Thr Arg Pro Pro Ser Ser Gln Pro Leu Asn Pro Arg Leu His Arg
20 25 30

Arg Trp Leu Ser Leu Gly Thr Trp Pro Arg Val Asp Asn Thr Trp Gly
35 40 45

Pro Leu Pro Asn Leu Pro Val Pro Gly Gly Ser His Pro Val Pro Pro
50 55 60

Ala Arg Met Cys Gln Pro Val Ser Ile Ser Glu Lys Ala Met Tyr Pro
65 70 75 80

Asp Tyr Phe Ala Lys Arg Glu Gln Trp Lys Lys Leu Arg Arg Glu Ser
85 90 95

Trp Glu Arg Glu Val Lys Gln Leu Gln Glu Glu Thr Pro Pro Gly Gly
100 105 110

Pro Leu Thr Glu Ala Leu Pro Pro Ala Arg Lys Glu Gly Asp Leu Pro
115 120 125

Pro Leu Val Val Val Tyr Cys Asp Gln Thr Pro Gly Ser Gly Pro Cys
130 135 140

Arg Lys Arg Glu Thr His Leu Ser Cys Leu Gln Val Lys
145 150 155

<210> 76
<211> 153
<212> PRT
<213> Homo sapien

<400> 76

Ser Trp Leu Gly Arg Glu Pro Ser Glu Gly Met Trp Thr Arg Lys Ala
1 5 10 15

Gly Arg Leu Arg Leu Gly Ser Arg Pro Ala Pro Thr Arg Pro Pro Ser
20 25 30

Ser Gln Pro Leu Asn Pro Arg Leu His Arg Arg Trp Leu Ser Leu Gly
35 40 45

Thr Trp Pro Arg Val Asp Asn Thr Trp Gly Pro Leu Pro Asn Leu Pro
50 55 60

Val Pro Gly Gly Ser His Pro Val Pro Pro Ala Arg Met Cys Gln Pro
65 70 75 80

Val Ser Ile Ser Glu Lys Ala Met Tyr Pro Asp Tyr Phe Ala Lys Arg
85 90 95

Glu Gln Trp Lys Lys Leu Arg Arg Glu Ser Trp Glu Arg Glu Val Lys
100 105 110

Gln Leu Gln Glu Glu Thr Pro Pro Gly Gly Pro Leu Thr Glu Ala Leu
115 120 125

Pro Pro Ala Arg Lys Glu Gly Asp Leu Pro Pro Leu Val Val Val Tyr
130 135 140

Cys Asp Gln Thr Pro Gly Ala Ala Met
145 150

<210> 77
<211> 73
<212> PRT
<213> Homo sapien

<400> 77

Met Gly Val Leu Gly Thr Val Arg Val Pro Thr Pro Ser Pro Gly Asn
1 5 10 15

Cys Ile Gly Gln Thr Phe Ala Met Ala Glu Met Lys Val Val Leu Ala
20 25 30

Leu Thr Leu Leu Arg Phe Arg Val Leu Pro Asp His Ala Glu Pro Arg
35 40 45

Arg Lys Leu Glu Leu Ile Val Arg Ala Glu Asp Gly Leu Trp Leu Arg
50 55 60

Val Glu Pro Leu Ser Ala Asp Leu Gln
65 70

<210> 78
<211> 199
<212> PRT
<213> Homo sapien

<400> 78

Glu Val Pro Gly Gly Arg Leu Lys Gly Asp Arg Arg Arg Ala Val Gln
1 5 10 15

Asp Leu Gly Ala Gly Cys Arg Gly Arg Gly Gly Lys Gly Arg Arg

72

20

25

30

Thr Gly Arg Ala Asp Lys Trp Val Gly Pro Leu Glu Val Arg Gly Gln
35 40 45

Gly Trp Ser Pro Gly Thr Lys Lys Gly Arg Gly Ser Ala Arg Pro Glu
50 55 60

Glu Trp Glu Glu Met Gly Pro Gly Cys Arg Val Pro Arg Gly Leu Gly
65 70 75 80

Gln Gly Pro Arg Cys Arg Arg Lys Met Arg Glu Phe Gly Phe Gly Asp
85 90 95

Leu Val His Pro Gly Pro Val Leu Pro Pro Leu Pro Pro Gln Arg Arg
100 105 110

Ala Ser Cys Ile Pro Phe Leu Trp Pro Glu Gly Ser Ser Val His Pro
115 120 125

Ser Gln Ala Leu Ala Ser Ser His Ser Pro Ala Leu Gly Pro Ile Arg
130 135 140

Leu Gly Arg Met Gly Glu Pro Val Val Ala Pro Gly Arg Gly Lys Gly
145 150 155 160

Gly Arg Leu Gly Lys Pro Leu Leu Gly Arg Thr Gln Tyr Ser Gly Ser
165 170 175

Ser Leu Ser Gly Lys Glu Arg Ile Trp Gly Lys Asn Gly Ser Ala Ser
180 185 190

His Ala Leu Thr Gly Glu Pro
195

<210> 79
<211> 132
<212> PRT
<213> Homo sapien

<400> 79

Ile Thr Phe Gln Glu His Leu Asn Gly Pro Leu Pro Val Pro Phe Thr
1 5 10 15

Asn Gly Glu Ile Gln Lys Glu Asn Ser Arg Glu Ala Leu Ala Glu Ala
20 25 30

Ala Leu Glu Ser Pro Arg Pro Asp Leu Val Arg Ile Arg Thr Pro Trp
35 40 45

Leu Ile Pro Lys Lys Glu Leu Asn Phe His Asn Asp Met Ser Pro Leu
50 55 60

Glu Glu Ser Arg Tyr Ser Thr Ala Thr Arg Arg Ser Tyr His Pro Ser
65 70 75 80

Ser Asp Pro Ile Leu Asp Phe Asn Ile Ser Leu Val Met Cys Leu Ser
85 90 95

Glu Arg Ala Ser Pro Gly Asn Ala Val Ser Lys Arg Ala Pro Gln Met
100 105 110

Asp Trp Ser Lys Lys Asn Glu Leu Phe Ser Glu Pro Leu Ser Ala Leu
115 120 125

Leu Pro Leu Gln
130

<210> 80
<211> 66
<212> PRT
<213> Homo sapien

<400> 80

Ala Ser Asp Ser His Arg Thr Pro Phe Ser Phe Ser Pro Ile Thr Pro
1 5 10 15

Leu Arg Ser Met Tyr Lys Ser Val Thr Arg Cys Ser Phe Leu Asp Ile
20 25 30

Met Met Ser Ser Arg Glu Leu Cys Ser Ser Arg Asp Phe Arg Glu Gly
35 40 45

Glu Cys Val Pro Ser Ser Arg Ser His Glu Arg Arg Leu Trp Leu Pro
50 55 60

Pro Pro
65

<210> 81
<211> 175
<212> PRT
<213> Homo sapien

74

<400> 81

Met Val Lys Leu Thr Ala Glu Leu Ile Glu Gln Ala Ala Gln Tyr Thr
1 5 10 15

Asn Ala Val Arg Asp Arg Glu Leu Asp Leu Arg Gly Tyr Lys Ile Pro
20 25 30

Val Ile Glu Asn Leu Gly Ala Thr Leu Asp Gln Phe Asp Ala Ile Asp
35 40 45

Phe Ser Asp Asn Glu Ile Arg Lys Leu Asp Gly Phe Pro Leu Leu Arg
50 55 60

Arg Leu Lys Thr Leu Leu Val Asn Asn Asn Arg Ile Cys Arg Ile Gly
65 70 75 80

Glu Gly Leu Asp Gln Ala Leu Pro Cys Leu Thr Glu Leu Ile Leu Thr
85 90 95

Asn Asn Ser Leu Val Glu Leu Gly Asp Leu Asp Pro Leu Ala Ser Leu
100 105 110

Lys Ser Leu Thr Tyr Leu Ser Ile Leu Arg Asn Pro Val Thr Asn Lys
115 120 125

Lys His Tyr Arg Leu Tyr Val Ile Tyr Lys Val Pro Gln Val Arg Val
130 135 140

Leu Asp Phe Gln Lys Val Lys Leu Lys Val Ser Ser Asn Leu Leu Leu
145 150 155 160

Val Ser His Tyr Arg Val Val Cys Phe Ser Leu Tyr Phe Cys Tyr
165 170 175

<210> 82

<211> 79

<212> PRT

<213> Homo sapien

<400> 82

Met Asp Val Ala Ala Glu Val Glu Val Leu Pro Lys Pro Arg Met Arg
1 5 10 15

Gly Leu Leu Ala Arg Arg Leu Arg Asn His Met Ala Val Ala Phe Val
20 25 30

75

Leu Ser Leu Gly Val Ala Ala Leu Tyr Lys Phe Arg Val Ala Asp Gln
35 40 45

Arg Lys Lys Ala Tyr Ala Asp Phe Tyr Arg Asn Tyr Asp Val Met Lys
50 55 60

Asp Phe Glu Glu Met Arg Lys Ala Gly Ile Phe Gln Ser Val Lys
65 70 75

<210> 83

<211> 88

<212> PRT

<213> Homo sapien

<400> 83

Met Leu Glu Arg Arg Gln Cys Asp Gly Cys Val Val Ala Ala Glu Val
1 5 10 15

Glu Val Leu Pro Lys Pro Arg Met Arg Gly Leu Leu Ala Arg Arg Leu
20 25 30

Arg Asn His Met Ala Val Ala Phe Val Leu Ser Leu Gly Val Ala Ala
35 40 45

Leu Tyr Lys Phe Arg Val Ala Asp Gln Arg Lys Lys Ala Tyr Ala Asp
50 55 60

Phe Tyr Arg Asn Tyr Asp Val Met Lys Asp Phe Glu Glu Met Arg Lys
65 70 75 80

Ala Gly Ile Phe Gln Ser Val Lys
85

<210> 84

<211> 93

<212> PRT

<213> Homo sapien

<400> 84

Met Leu Glu Arg Arg Ser Val Met Asp Ala Trp Ser Arg Ala Gly Val
1 5 10 15

Thr Thr Met Ala Pro Glu Val Leu Pro Lys Pro Arg Met Arg Gly Leu
20 25 30

Leu Ala Arg Arg Leu Arg Asn His Met Ala Val Ala Phe Val Leu Ser
35 40 45

Leu Gly Val Ala Ala Leu Tyr Lys Phe Arg Val Ala Asp Gln Arg Lys
50 55 60

Lys Ala Tyr Ala Asp Phe Tyr Arg Asn Tyr Asp Val Met Lys Asp Phe
65 70 75 80

Glu Glu Met Arg Lys Ala Gly Ile Phe Gln Ser Val Lys
85 90

<210> 85
<211> 80
<212> PRT
<213> Homo sapien

<400> 85

Met Asp Arg Gly Arg Gly Glu Val Glu Val Leu Pro Lys Pro Arg Met
1 5 10 15

Arg Gly Leu Leu Ala Arg Arg Leu Arg Asn His Met Ala Val Ala Phe
20 25 30

Val Leu Ser Leu Gly Val Ala Ala Leu Tyr Lys Phe Arg Val Ala Asp
35 40 45

Gln Arg Lys Lys Ala Tyr Ala Asp Phe Tyr Arg Asn Tyr Asp Val Met
50 55 60

Lys Asp Phe Glu Glu Met Arg Lys Ala Gly Ile Phe Gln Ser Val Lys
65 70 75 80

<210> 86
<211> 68
<212> PRT
<213> Homo sapien

<400> 86

Met Trp Ser Arg Pro Arg Phe Leu Ala Arg Arg Leu Arg Asn His Met
1 5 10 15

Ala Val Ala Phe Val Leu Ser Leu Gly Val Ala Ala Leu Tyr Lys Phe
20 25 30

Arg Val Ala Asp Gln Arg Lys Lys Ala Tyr Ala Asp Phe Tyr Arg Asn
35 40 45

Tyr Asp Val Met Lys Asp Phe Glu Glu Met Arg Lys Ala Gly Ile Phe
50 55 60

Gln Ser Val Lys
65

<210> 87
<211> 53
<212> PRT
<213> Homo sapien

<400> 87

Met Ala Val Ala Phe Val Leu Ser Leu Gly Val Ala Ala Leu Tyr Lys
1 5 10 15

Phe Arg Val Ala Asp Gln Arg Lys Lys Ala Tyr Ala Asp Phe Tyr Arg
20 25 30

Asn Tyr Asp Val Met Lys Asp Phe Glu Glu Met Arg Lys Ala Gly Ile
35 40 45

Phe Gln Ser Val Lys
50

<210> 88
<211> 72
<212> PRT
<213> Homo sapien

<400> 88

Trp Ile Gly Arg Pro Gly Arg Ser Asn Val Gln Leu Ser Leu Arg Ser
1 5 10 15

Trp Asp Leu Gly Pro Thr Val Trp Pro Phe Ser Leu Gln Ala Val Leu
20 25 30

Gly Leu Lys Phe Arg Val Ala Asp Gln Arg Lys Lys Ala Tyr Ala Asp
35 40 45

Phe Tyr Arg Asn Tyr Asp Val Met Lys Asp Phe Glu Glu Met Arg Lys
50 55 60

Ala Gly Ile Phe Gln Ser Val Lys
65 70

<210> 89
<211> 80
<212> PRT
<213> Homo sapien

78

<400> 89

Met Leu Glu Ala Ala Gln Cys Asp Gly Ser Ala Ala Arg Ala Gly Gln
1 5 10 15

Met Cys Ser Ser Pro Ser Gly Ser Trp Asp Leu Gly Pro Thr Val Trp
20 25 30

Pro Phe Ser Leu Gln Ala Val Leu Gly Leu Lys Phe Arg Val Ala Asp
35 40 45

Gln Arg Lys Lys Ala Tyr Ala Asp Phe Tyr Arg Asn Tyr Asp Val Met
50 55 60

Lys Asp Phe Glu Glu Met Arg Lys Ala Gly Ile Phe Gln Ser Val Lys
65 70 75 80

<210> 90
<211> 174
<212> PRT
<213> Homo sapien

<220>
<221> MISC_FEATURE
<222> (13)..(14)
<223> X=any amino acid

<400> 90

Gln Ile Lys Lys Lys Lys Lys Lys Lys Lys Lys Xaa Xaa Lys Lys
1 5 10 15

Asn Thr Lys Lys His Lys Lys Lys Arg Gly Gly Arg Pro Thr Lys Tyr
20 25 30

Pro Pro Gly Gly Asp Ala Gln Thr Ser Asn Pro Pro Phe Gly Lys Arg
35 40 45

Gly Pro Pro Gln Glu Gly Ala Gln Lys Thr Ala Ala Gly Gly Asn Lys
50 55 60

Arg Arg Ala Asp Lys Pro Ser Ala Arg Gly Gln Arg Glu Arg Gln Thr
65 70 75 80

Pro His Arg Arg Gly Gly Asp Arg Pro Gly Ala Pro Thr Pro Pro Thr
85 90 95

Glu Gln Thr Arg Arg Ala Lys Thr Thr Thr Ala Arg Asp Val Gly
100 105 110

Gln Pro Thr Ala Arg Ser Ala Ala Thr Ala Ala Leu Thr Leu Ser Gly
115 120 125

Thr Ile Gln Gly Ala Ala Ile Asn Arg Ala His Thr Pro Ala Ser Gln
130 135 140

Thr Thr Arg Arg Pro Pro His Ala Asp Ala Thr Thr Pro Arg Pro Thr
145 150 155 160

Asn Tyr Gly Ser Ser Ala Gln Asn Leu Ala Thr Pro Pro His
165 170

<210> 91
<211> 101
<212> PRT
<213> Homo sapien

<400> 91

Met Asp Arg Gly Arg Gly Glu Val Ser Gly Arg Thr Leu Val Leu Arg
1 5 10 15

Leu Ala Tyr Val Ser Arg Thr Val Thr Thr Met Ala Pro Glu Val Leu
20 25 30

Pro Lys Pro Arg Met Arg Gly Leu Leu Ala Arg Arg Leu Arg Asn His
35 40 45

Met Ala Val Ala Phe Val Leu Ser Leu Gly Val Ala Ala Leu Tyr Lys
50 55 60

Phe Arg Val Ala Asp Gln Arg Lys Lys Ala Tyr Ala Asp Phe Tyr Arg
65 70 75 80

Asn Tyr Asp Val Met Lys Asp Phe Glu Glu Met Arg Lys Ala Gly Ile
85 90 95

Phe Gln Ser Val Lys
100

<210> 92
<211> 216
<212> PRT
<213> Homo sapien

<400> 92

Met Val Ser Thr Asn Phe Thr Ser Gly Ser Arg Cys His Gly Cys Pro

1	5	10	15
Lys Ser Leu Glu Thr Thr Thr Ser Pro Leu Pro Arg Arg Trp Arg Arg			
20	25	30	
Pro Gly Ala Val Trp Pro Arg Lys Pro Gly Asn Trp Pro Thr Thr Cys			
35	40	45	
Arg Lys Leu Arg Val Ser Met Lys Ser Thr Asn Thr Thr Arg Asn Ser			
50	55	60	
Ser Lys Lys Ser Trp Arg Arg Ser Pro Gly Leu Arg Arg Ser His His			
65	70	75	80
Tyr Phe Lys Tyr Cys Lys Ile Ser Ala Leu Ala Leu Leu Lys Met Val			
85	90	95	
Met His Ala Arg Ser Gly Gly Asn Leu Glu Val Met Gly Leu Met Leu			
100	105	110	
Gly Lys Val Asp Gly Glu Thr Met Ile Ile Met Asp Ser Phe Ala Leu			
115	120	125	
Pro Val Glu Gly Thr Glu Thr Arg Val Asn Ala Gln Ala Ala Ala Tyr			
130	135	140	
Glu Tyr Met Ala Ala Tyr Ile Glu Asn Ala Lys Gln Val Gly Arg Leu			
145	150	155	160
Glu Asn Ala Ile Gly Trp Tyr His Ser His Pro Gly Tyr Gly Cys Trp			
165	170	175	
Leu Ser Gly Ile Asp Val Ser Thr Gln Met Leu Asn Gln Gln Phe Gln			
180	185	190	
Glu Pro Phe Val Ala Val Val Ile Asp Pro Thr Arg Thr Ile Ser Ala			
195	200	205	
Gly Lys Ser Glu Ser Trp Arg Leu			
210	215		
<210> 93			
<211> 352			
<212> PRT			
<213> Homo sapien			
<400> 93			

81

Val Ser Trp Leu Pro Gln Glu Ser Arg Asp Asp Asn Phe Ser Ala Ser
1 5 10 15

Ser Ala Met Ala Ala Ser Gly Ser Gly Met Ala Gln Lys Thr Trp Glu
20 25 30

Leu Ala Asn Asn Met Gln Glu Ala Gln Ser Ile Asp Glu Ile Tyr Lys
35 40 45

Tyr Asp Lys Lys Gln Gln Glu Ile Leu Ala Ala Lys Pro Trp Thr
50 55 60

Lys Asp His His Tyr Phe Lys Tyr Cys Lys Ile Ser Ala Leu Ala Leu
65 70 75 80

Leu Lys Met Val Met His Ala Arg Ser Gly Gly Asn Leu Glu Val Met
85 90 95

Gly Leu Met Leu Gly Lys Val Asp Gly Glu Thr Met Ile Ile Met Asp
100 105 110

Ser Phe Ala Leu Pro Val Glu Gly Thr Glu Thr Arg Val Asn Ala Gln
115 120 125

Ala Ala Ala Tyr Glu Tyr Met Ala Ala Tyr Ile Glu Asn Ala Lys Gln
130 135 140

Val Gly Arg Leu Glu Asn Ala Ile Gly Trp Tyr His Ser His Pro Gly
145 150 155 160

Tyr Gly Cys Trp Leu Ser Gly Ile Asp Val Ser Thr Gln Met Leu Asn
165 170 175

Gln Gln Phe Gln Glu Pro Phe Val Ala Val Val Ile Asp Pro Thr Arg
180 185 190

Thr Ile Ser Ala Gly Lys Val Asn Leu Gly Ala Phe Arg Thr Tyr Pro
195 200 205

Lys Gly Tyr Lys Pro Pro Asp Glu Gly Pro Ser Glu Tyr Gln Thr Ile
210 215 220

Pro Leu Asn Lys Ile Glu Asp Phe Gly Val His Cys Lys Gln Tyr Tyr
225 230 235 240

82

Ala Leu Glu Val Ser Tyr Phe Lys Ser Ser Leu Asp Arg Lys Leu Leu
245 250 255

Glu Leu Leu Trp Asn Lys Tyr Trp Val Asn Thr Leu Ser Ser Ser Ser
260 265 270

Leu Leu Thr Asn Ala Asp Tyr Thr Thr Gly Gln Val Phe Asp Leu Ser
275 280 285

Glu Lys Leu Glu Gln Ser Glu Ala Gln Leu Gly Arg Gly Ser Phe Met
290 295 300

Leu Gly Leu Glu Thr His Asp Arg Lys Ser Glu Asp Lys Leu Ala Lys
305 310 315 320

Ala Thr Arg Asp Ser Cys Lys Thr Thr Ile Glu Ala Ile His Gly Leu
325 330 335

Met Ser Gln Val Ile Lys Asp Lys Leu Phe Asn Gln Ile Asn Ile Ser
340 345 350

<210> 94
<211> 72
<212> PRT
<213> Homo sapien

<400> 94

Met Ala Gln Lys Thr Trp Glu Leu Ala Asn Asn Met Gln Glu Ala Gln
1 5 10 15

Ser Ile Asp Glu Ile Tyr Lys Tyr Asp Lys Lys Gln Gln Gln Glu Ile
20 25 30

Leu Ala Ala Lys Pro Trp Thr Lys Lys Asp Lys Gly Arg Ser Gln Asp
35 40 45

Phe Asp Ser Cys Leu Asp Phe Gln His Glu Val Tyr Thr Phe Phe Ser
50 55 60

Phe Trp Leu Lys Ser Gly Lys Ala
65 70

<210> 95
<211> 292
<212> PRT
<213> Homo sapien

<400> 95

Gln Ala Val His Phe Ser His His Tyr Phe Lys Tyr Cys Lys Ile Ser
1 5 10 15

Ala Leu Ala Leu Leu Lys Met Val Met His Ala Arg Ser Gly Gly Asn
20 25 30

Leu Glu Val Met Gly Leu Met Leu Gly Lys Val Asp Gly Glu Thr Met
35 40 45

Ile Ile Met Asp Ser Phe Ala Leu Pro Val Glu Gly Thr Glu Thr Arg
50 55 60

Val Asn Ala Gln Ala Ala Ala Tyr Glu Tyr Met Ala Ala Tyr Ile Glu
65 70 75 80

Asn Ala Lys Gln Val Gly Arg Leu Glu Asn Ala Ile Gly Trp Tyr His
85 90 95

Ser His Pro Gly Tyr Gly Cys Trp Leu Ser Gly Ile Asp Val Ser Thr
100 105 110

Gln Met Leu Asn Gln Gln Phe Gln Glu Pro Phe Val Ala Val Val Ile
115 120 125

Asp Pro Thr Arg Thr Ile Ser Ala Gly Lys Val Asn Leu Gly Ala Phe
130 135 140

Arg Thr Tyr Pro Lys Gly Tyr Lys Pro Pro Asp Glu Gly Pro Ser Glu
145 150 155 160

Tyr Gln Thr Ile Pro Leu Asn Lys Ile Glu Asp Phe Gly Val His Cys
165 170 175

Lys Gln Tyr Tyr Ala Leu Glu Val Ser Tyr Phe Lys Ser Ser Leu Asp
180 185 190

Arg Lys Leu Leu Glu Leu Leu Trp Asn Lys Tyr Trp Val Asn Thr Leu
195 200 205

Ser Ser Ser Ser Leu Leu Thr Asn Ala Asp Tyr Thr Thr Gly Gln Val
210 215 220

Phe Asp Leu Ser Glu Lys Leu Glu Gln Ser Glu Ala Gln Leu Gly Arg
225 230 235 240

84

Gly Ser Phe Met Leu Gly Leu Glu Thr His Asp Arg Lys Ser Glu Asp
245 250 255

Lys Leu Ala Lys Ala Thr Arg Asp Ser Cys Lys Thr Thr Ile Glu Ala
260 265 270

Ile His Gly Leu Met Ser Gln Val Ile Lys Asp Lys Leu Phe Asn Gln
275 280 285

Ile Asn Ile Ser
290

<210> 96
<211> 158
<212> PRT
<213> Homo sapien

<400> 96

Met Val Ser Thr Asn Phe Thr Ser Gly Ser Arg Cys His Gly Cys Pro
1 5 10 15

Lys Ser Leu Gly His His Tyr Phe Lys Tyr Cys Lys Ile Ser Ala Leu
20 25 30

Ala Leu Leu Lys Met Val Met His Ala Arg Ser Gly Gly Asn Leu Glu
35 40 45

Val Met Gly Leu Met Leu Gly Lys Val Asp Gly Glu Thr Met Ile Ile
50 55 60

Met Asp Ser Phe Ala Leu Pro Val Glu Gly Thr Glu Thr Arg Val Asn
65 70 75 80

Ala Gln Ala Ala Ala Tyr Glu Tyr Met Ala Ala Tyr Ile Glu Asn Ala
85 90 95

Lys Gln Val Gly Arg Leu Glu Asn Ala Ile Gly Trp Tyr His Ser His
100 105 110

Pro Gly Tyr Gly Cys Trp Leu Ser Gly Ile Asp Val Ser Thr Gln Met
115 120 125

Leu Asn Gln Gln Phe Gln Glu Pro Phe Val Ala Val Val Ile Asp Pro
130 135 140

Thr Arg Thr Ile Ser Ala Gly Lys Ser Glu Ser Trp Arg Leu
145 150 155

<210> 97
<211> 295
<212> PRT
<213> Homo sapien

<400> 97

Val Ser Trp Leu Pro Gln Glu Ser Ser His His Tyr Phe Lys Tyr Cys
1 5 10 15

Lys Ile Ser Ala Leu Ala Leu Leu Lys Met Val Met His Ala Arg Ser
20 25 30

Gly Gly Asn Leu Glu Val Met Gly Leu Met Leu Gly Lys Val Asp Gly
35 40 45

Glu Thr Met Ile Ile Met Asp Ser Phe Ala Leu Pro Val Glu Gly Thr
50 55 60

Glu Thr Arg Val Asn Ala Gln Ala Ala Ala Tyr Glu Tyr Met Ala Ala
65 70 75 80

Tyr Ile Glu Asn Ala Lys Gln Val Gly Arg Leu Glu Asn Ala Ile Gly
85 90 95

Trp Tyr His Ser His Pro Gly Tyr Gly Cys Trp Leu Ser Gly Ile Asp
100 105 110

Val Ser Thr Gln Met Leu Asn Gln Gln Phe Gln Glu Pro Phe Val Ala
115 120 125

Val Val Ile Asp Pro Thr Arg Thr Ile Ser Ala Gly Lys Val Asn Leu
130 135 140

Gly Ala Phe Arg Thr Tyr Pro Lys Gly Tyr Lys Pro Pro Asp Glu Gly
145 150 155 160

Pro Ser Glu Tyr Gln Thr Ile Pro Leu Asn Lys Ile Glu Asp Phe Gly
165 170 175

Val His Cys Lys Gln Tyr Tyr Ala Leu Glu Val Ser Tyr Phe Lys Ser
180 185 190

Ser Leu Asp Arg Lys Leu Leu Glu Leu Leu Trp Asn Lys Tyr Trp Val
195 200 205

86

Asn Thr Leu Ser Ser Ser Ser Leu Leu Thr Asn Ala Asp Tyr Thr Thr
210 215 220

Gly Gln Val Phe Asp Leu Ser Glu Lys Leu Glu Gln Ser Glu Ala Gln
225 230 235 240

Leu Gly Arg Gly Ser Phe Met Leu Gly Leu Glu Thr His Asp Arg Lys
245 250 255

Ser Glu Asp Lys Leu Ala Lys Ala Thr Arg Asp Ser Cys Lys Thr Thr
260 265 270

Ile Glu Ala Ile His Gly Leu Met Ser Gln Val Ile Lys Asp Lys Leu
275 280 285

Phe Asn Gln Ile Asn Ile Ser
290 295

<210> 98
<211> 152
<212> PRT
<213> Homo sapien

<400> 98

Met Lys Ser Thr Asn Thr Thr Arg Asn Ser Ser Lys Lys Ser Trp Arg
1 5 10 15

Arg Ser Pro Gly Leu Arg Arg Ser His His Tyr Phe Lys Tyr Cys Lys
20 25 30

Ile Ser Ala Leu Ala Leu Leu Lys Met Val Met His Ala Arg Ser Gly
35 40 45

Gly Asn Leu Glu Val Met Gly Leu Met Leu Gly Lys Val Asp Gly Glu
50 55 60

Thr Met Ile Ile Met Asp Ser Phe Ala Leu Pro Val Glu Gly Thr Glu
65 70 75 80

Thr Arg Val Asn Ala Gln Ala Ala Tyr Glu Tyr Met Ala Ala Tyr
85 90 95

Ile Glu Asn Ala Lys Gln Val Gly Arg Leu Glu Asn Ala Ile Gly Trp
100 105 110

Tyr His Ser His Pro Gly Tyr Gly Cys Trp Leu Ser Gly Ile Asp Val
115 120 125

Ser Thr Gln Met Leu Asn Gln Gln Phe Gln Glu Pro Phe Val Ala Val
130 135 140

Val Val Thr Met Gly Lys Ala Ala
145 150

<210> 99
<211> 211
<212> PRT
<213> Homo sapien

<400> 99

Glu Phe Val Pro Val Val Arg Arg Val Lys Ala His Thr Arg Lys Pro
1 5 10 15

Ser Glu Val Lys Leu Arg Leu Gly Cys Arg Asp Asp Asn Phe Ser Ala
20 25 30

Ser Ser Ala Met Ala Ala Ser Gly Ser Gly Met Ala Gln Lys Thr Trp
35 40 45

Glu Leu Ala Asn Asn Met Gln Glu Ala Gln Ser Ile Asp Glu Ile Tyr
50 55 60

Lys Tyr Asp Lys Lys Gln Gln Glu Ile Leu Ala Ala Lys Pro Trp
65 70 75 80

Thr Lys Asp His His Tyr Phe Lys Tyr Cys Lys Ile Ser Ala Leu Ala
85 90 95

Leu Leu Lys Met Val Met His Ala Arg Ser Gly Gly Asn Leu Glu Val
100 105 110

Met Gly Leu Met Leu Gly Lys Val Asp Gly Glu Thr Met Ile Ile Met
115 120 125

Asp Ser Phe Ala Leu Pro Val Glu Gly Thr Glu Thr Arg Val Asn Ala
130 135 140

Gln Ala Ala Ala Tyr Glu Tyr Met Ala Ala Tyr Ile Glu Asn Ala Lys
145 150 155 160

Gln Val Gly Arg Leu Glu Asn Ala Ile Gly Trp Tyr His Ser His Pro
165 170 175

88

Gly Tyr Gly Cys Trp Leu Ser Gly Ile Asp Val Ser Thr Gln Met Leu
180 185 190

Asn Gln Gln Phe Gln Glu Pro Phe Val Ala Val Val Val Thr Met Gly
195 200 205

Lys Ala Ala
210

<210> 100
<211> 149
<212> PRT
<213> Homo sapien

<400> 100

Leu Arg Arg Ser Phe Ile Arg Arg Phe Val Ala Leu Trp Val Cys Pro
1 5 10 15

Lys Gly Ala Asn Ile Pro Leu Asn Lys Ile Glu Asp Phe Gly Val His
20 25 30

Cys Lys Gln Tyr Tyr Ala Leu Glu Val Ser Tyr Phe Lys Ser Ser Leu
35 40 45

Asp Arg Lys Leu Leu Glu Leu Leu Trp Asn Lys Tyr Trp Val Asn Thr
50 55 60

Leu Ser Ser Ser Ser Leu Leu Thr Asn Ala Asp Tyr Thr Thr Gly Gln
65 70 75 80

Val Phe Asp Leu Ser Glu Lys Leu Glu Gln Ser Glu Ala Gln Leu Gly
85 90 95

Arg Gly Ser Phe Met Leu Gly Leu Glu Thr His Asp Arg Lys Ser Glu
100 105 110

Asp Lys Leu Ala Lys Ala Thr Arg Asp Ser Cys Lys Thr Thr Ile Glu
115 120 125

Ala Ile His Gly Leu Met Ser Gln Val Ile Lys Asp Lys Leu Phe Asn
130 135 140

Gln Ile Asn Ile Ser
145

<210> 101
<211> 199

89

<212> PRT

<213> Homo sapien

<400> 101

Met Ser Ser Gly Asn Ala Lys Ile Gly His Pro Ala Pro Asn Phe Lys
1 5 10 15

Ala Thr Ala Val Met Pro Asp Gly Gln Phe Lys Asp Ile Ser Leu Ser
20 25 30

Asp Tyr Lys Gly Lys Tyr Val Val Phe Phe Tyr Pro Leu Asp Phe
35 40 45

Thr Phe Val Cys Pro Thr Glu Ile Ile Ala Phe Ser Asp Arg Ala Glu
50 55 60

Glu Phe Lys Lys Leu Asn Cys Gln Val Ile Gly Ala Ser Val Asp Ser
65 70 75 80

His Phe Cys His Leu Ala Trp Val Asn Thr Pro Lys Lys Gln Gly Gly
85 90 95

Leu Gly Pro Met Asn Ile Pro Leu Val Ser Asp Pro Lys Arg Thr Ile
100 105 110

Ala Gln Asp Tyr Gly Val Leu Lys Ala Asp Glu Gly Ile Ser Phe Arg
115 120 125

Gly Leu Phe Ile Ile Asp Asp Lys Gly Ile Leu Arg Gln Ile Thr Val
130 135 140

Asn Asp Leu Pro Val Gly Arg Ser Val Asp Glu Thr Leu Arg Leu Val
145 150 155 160

Gln Ala Phe Gln Phe Thr Asp Lys His Gly Glu Val Cys Pro Ala Gly
165 170 175

Trp Lys Pro Gly Ser Asp Thr Ile Lys Pro Asp Val Gln Lys Ser Lys
180 185 190

Glu Tyr Phe Ser Lys Gln Lys
195

<210> 102

<211> 49

<212> PRT

<213> Homo sapien

90

<400> 102

Ser Pro His Val Gln Pro Pro Asp Trp Gly Thr Gly Thr Gln Pro Glu
1 5 10 15

Ser Ala Ser Cys Val Leu Gln Ala Gly Ala Glu Ile Ser Thr Val Asn
20 25 30

Pro Glu Gln Tyr Ser Lys Arg Phe Asn Glu Phe Met Ser Asn Ile Leu
35 40 45

Thr

<210> 103

<211> 132

<212> PRT

<213> Homo sapien

<400> 103

Thr Thr Leu Arg Ala Leu Ala Leu Asn Leu Trp Pro Pro Lys Ser Arg
1 5 10 15

Ser Leu Ile Ser Ser Trp Gln Ser Cys Gly Gln Glu Val Leu Lys Gly
20 25 30

Lys Thr His Ser Asp Asn Cys Ser Pro Ile Tyr Gln Pro Ser Ala Gly
35 40 45

Val Ser Asp Arg Gly Pro Leu Pro Pro Leu Glu Cys Ala Thr Tyr Glu
50 55 60

Glu Cys Pro Met Gly Lys Arg Arg Leu Ser Cys Pro Leu Ala Ala Cys
65 70 75 80

Ala Ser Ile Pro Gly Gln Lys Phe Pro Gln Glu Pro Leu Ala Leu Ala
85 90 95

Gln Ser His Cys Glu Arg Arg Trp Glu Pro Thr Pro Leu Gly Glu Gly
100 105 110

Ala Val Leu Leu Gly Thr Ser Gln His Gln Val Arg Ser Leu Lys Leu
115 120 125

Lys Asn Val Asn
130

<210> 104
<211> 71
<212> PRT
<213> Homo sapien

<400> 104

Met Arg Ser Arg Asn Phe Ala Gly Gly Gln Arg Gly Trp Arg Cys Asp
1 5 10 15

Asn Cys Arg Arg Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly
20 25 30

Gln Ser Tyr Asn Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr
35 40 45

Asn Val Asn Cys Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala
50 55 60

Asp Arg Glu Asp Ser Arg Glu
65 70

<210> 105
<211> 177
<212> PRT
<213> Homo sapien

<400> 105

Met Lys Val Phe Cys Asn Met Glu Thr Gly Glu Thr Cys Val Tyr Pro
1 5 10 15

Asn Pro Ala Asn Val Pro Lys Lys Asn Trp Trp Ser Ser Lys Ser Lys
20 25 30

Glu Lys Lys His Ile Trp Phe Gly Glu Thr Ile Asn Gly Gly Phe His
35 40 45

Phe Ser Tyr Gly Asp Asp Asn Leu Ala Pro Asn Thr Ala Asn Val Gln
50 55 60

Met Thr Phe Leu Arg Leu Leu Ser Thr Glu Gly Ser Gln Asn Ile Thr
65 70 75 80

Tyr His Cys Lys Asn Ser Ile Ala Tyr Leu Asp Glu Ala Ala Gly Asn
85 90 95

Leu Lys Lys Ala Leu Leu Ile Gln Gly Ser Asn Asp Val Glu Ile Arg
100 105 110

Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Ala Leu Lys Asp Gly Cys
115 120 125

Thr Lys His Thr Gly Lys Trp Gly Lys Thr Val Ile Glu Tyr Arg Ser
130 135 140

Gln Lys Thr Ser Arg Leu Pro Ile Ile Asp Ile Ala Pro Met Asp Ile
145 150 155 160

Gly Gly Pro Glu Gln Glu Phe Gly Val Asp Ile Gly Pro Val Cys Phe
165 170 175

Leu

<210> 106

<211> 175

<212> PRT

<213> Homo sapien

<400> 106

Met Asn Ser Ile Ala Ser Val Arg Asp Thr His Phe Pro Gly Pro Asp
1 5 10 15

Leu Ile Gly Ile Ser Val Ala Thr Asp Ser Ile Cys Glu Leu Ile Gln
20 25 30

Tyr Ile Thr Arg Tyr Ile Ala Ser Leu Lys Gln Arg Tyr Thr Gln Ser
35 40 45

Asn Gly Arg Arg Pro Phe Gly Ile Ser Ala Leu Ile Val Gly Phe Asp
50 55 60

Phe Asp Gly Thr Pro Arg Leu Tyr Gln Thr Asp Pro Ser Gly Thr Tyr
65 70 75 80

His Ala Trp Lys Ala Asn Ala Ile Gly Arg Gly Ala Lys Ser Val Arg
85 90 95

Glu Phe Leu Glu Lys Asn Tyr Thr Asp Glu Ala Ile Glu Thr Asp Asp
100 105 110

Leu Thr Ile Lys Leu Val Ile Lys Ala Leu Leu Glu Val Val Gln Ser
115 120 125

93

Gly Gly Lys Asn Ile Glu Leu Ala Val Met Arg Arg Asp Gln Ser Leu
130 135 140

Lys Ile Leu Asn Pro Glu Glu Ile Glu Lys Tyr Val Ala Glu Ile Glu
145 150 155 160

Lys Glu Lys Glu Glu Asn Glu Lys Lys Gln Lys Lys Ala Ser
165 170 175

<210> 107

<211> 501

<212> PRT

<213> Homo sapien

<400> 107

Met Trp Pro Ser Glu Ser Thr Trp Gly Ser Lys Phe Gln Ile Leu Ala
1 5 10 15

Ser Leu Val Pro Gly Arg Ala Tyr Lys Ser Arg Ala Ser Pro Phe Val
20 25 30

Thr Cys Ile Phe Phe Leu Pro Leu Cys Thr Leu Cys Leu Ser Leu Pro
35 40 45

Leu Ser Leu Phe Leu Cys Leu Leu Leu Trp Leu Ser Ser Pro Ser Ser
50 55 60

Leu Arg Ser Gln Asp Arg His Asp Gly Val Pro Ser His Ser Ser Arg
65 70 75 80

Leu Ser Gln Leu Gly Ser Val Ser Gln Gly Pro Tyr Ser Ser Ala Pro
85 90 95

Pro Leu Ser His Thr Pro Ser Ser Asp Phe Gln Pro Pro Tyr Phe Pro
100 105 110

Pro Pro Tyr Gln Pro Leu Pro Tyr His Gln Ser Gln Asp Pro Tyr Ser
115 120 125

His Val Asn Asp Pro Tyr Ser Leu Asn Pro Leu His Gln Pro Gln Gln
130 135 140

His Pro Trp Gly Gln Arg Gln Arg Gln Glu Val Gly Ser Glu Ala Gly
145 150 155 160

Ser Leu Leu Pro Gln Pro Arg Ala Ala Leu Pro Gln Leu Ser Gly Leu
165 170 175

Asp Pro Arg Arg Asp Tyr His Ser Val Arg Arg Pro Asp Val Leu Leu
180 185 190

His Ser Ala His His Gly Leu Asp Ala Gly Met Gly Asp Ser Leu Ser
195 200 205

Leu His Gly Leu Gly His Pro Gly Met Glu Asp Val Gln Ser Val Glu
210 215 220

Asp Ala Asn Asn Ser Gly Met Asn Leu Leu Asp Gln Ser Val Ile Lys
225 230 235 240

Lys Val Pro Val Pro Pro Lys Ser Val Thr Ser Leu Met Met Asn Lys
245 250 255

Asp Gly Phe Leu Gly Gly Met Ser Val Asn Thr Gly Glu Val Phe Cys
260 265 270

Ser Val Pro Gly Arg Leu Ser Leu Leu Ser Ser Thr Ser Lys Tyr Lys
275 280 285

Val Thr Val Gly Glu Val Gln Arg Arg Leu Ser Pro Pro Glu Cys Leu
290 295 300

Asn Ala Ser Leu Leu Gly Gly Val Leu Arg Arg Ala Lys Ser Lys Asn
305 310 315 320

Gly Gly Arg Ser Leu Arg Glu Arg Leu Glu Lys Ile Gly Leu Asn Leu
325 330 335

Pro Ala Gly Arg Arg Lys Ala Ala Asn Val Thr Leu Leu Thr Ser Leu
340 345 350

Val Glu Gly Glu Ala Val His Leu Ala Arg Asp Phe Gly Tyr Ile Cys
355 360 365

Glu Thr Glu Phe Pro Ala Lys Ala Val Ser Glu Tyr Leu Asn Arg Gln
370 375 380

His Thr Asp Pro Ser Asp Leu His Ser Arg Lys Asn Met Leu Leu Ala
385 390 395 400

Thr Lys Gln Leu Cys Lys Glu Phe Thr Asp Leu Leu Ala Gln Asp Arg
405 410 415

Thr Pro Ile Gly Asn Ser Arg Pro Ser Pro Ile Leu Glu Pro Gly Ile
420 425 430

Gln Ser Cys Leu Thr His Phe Ser Leu Ile Thr His Gly Phe Gly Ala
435 440 445

Pro Ala Ile Cys Ala Ala Leu Thr Ala Leu Gln Asn Tyr Leu Thr Glu
450 455 460

Ala Leu Lys Gly Met Asp Lys Met Phe Leu Asn Asn Thr Thr Thr Asn
465 470 475 480

Arg His Thr Ser Gly Glu Gly Pro Gly Ser Lys Thr Gly Asp Lys Glu
485 490 495

Glu Lys His Arg Lys
500

<210> 108
<211> 458
<212> PRT
<213> Homo sapien

<400> 108

Met Leu Trp Lys Leu Val Glu Asn Val Lys Tyr Glu Asp Ile Tyr Glu
1 5 10 15

Met Leu Val His Thr Tyr Ser Ser Met Asp Arg His Asp Gly Val Pro
20 25 30

Ser His Ser Ser Arg Leu Ser Gln Leu Gly Ser Val Ser Gln Gly Pro
35 40 45

Tyr Ser Ser Ala Pro Pro Leu Ser His Thr Pro Ser Ser Asp Phe Gln
50 55 60

Pro Pro Tyr Phe Pro Pro Tyr Gln Pro Leu Pro Tyr His Gln Ser
65 70 75 80

Gln Asp Pro Tyr Ser His Val Asn Asp Pro Tyr Ser Leu Asn Pro Leu
85 90 95

His Gln Pro Gln Gln His Pro Trp Gly Gln Arg Gln Arg Gln Glu Val
100 105 110

Gly Ser Glu Ala Gly Ser Leu Leu Pro Gln Pro Arg Ala Ala Leu Pro

96

115

120

125

Gln Leu Ser Gly Leu Asp Pro Arg Arg Asp Tyr His Ser Val Arg Arg
130 135 140

Pro Asp Val Leu Leu His Ser Ala His His Gly Leu Asp Ala Gly Met
145 150 155 160

Gly Asp Ser Leu Ser Leu His Gly Leu Gly His Pro Gly Met Glu Asp
165 170 175

Val Gln Ser Val Glu Asp Ala Asn Asn Ser Gly Met Asn Leu Leu Asp
180 185 190

Gln Ser Val Ile Lys Lys Val Pro Val Pro Pro Lys Ser Val Thr Ser
195 200 205

Leu Met Met Asn Lys Asp Gly Phe Leu Gly Gly Met Ser Val Asn Thr
210 215 220

Gly Glu Val Phe Cys Ser Val Pro Gly Arg Leu Ser Leu Leu Ser Ser
225 230 235 240

Thr Ser Lys Tyr Lys Val Thr Val Gly Glu Val Gln Arg Arg Leu Ser
245 250 255

Pro Pro Glu Cys Leu Asn Ala Ser Leu Leu Gly Gly Val Leu Arg Arg
260 265 270

Ala Lys Ser Lys Asn Gly Gly Arg Ser Leu Arg Glu Arg Leu Glu Lys
275 280 285

Ile Gly Leu Asn Leu Pro Ala Gly Arg Arg Lys Ala Ala Asn Val Thr
290 295 300

Leu Leu Thr Ser Leu Val Glu Gly Glu Ala Val His Leu Ala Arg Asp
305 310 315 320

Phe Gly Tyr Ile Cys Glu Thr Glu Phe Pro Ala Lys Ala Val Ser Glu
325 330 335

Tyr Leu Asn Arg Gln His Thr Asp Pro Ser Asp Leu His Ser Arg Lys
340 345 350

Asn Met Leu Leu Ala Thr Lys Gln Leu Cys Lys Glu Phe Thr Asp Leu
355 360 365

Leu Ala Gln Asp Arg Thr Pro Ile Gly Asn Ser Arg Pro Ser Pro Ile
370 375 380

Leu Glu Pro Gly Ile Gln Ser Cys Leu Thr His Phe Ser Leu Ile Thr
385 390 395 400

His Gly Phe Gly Ala Pro Ala Ile Cys Ala Ala Leu Thr Ala Leu Gln
405 410 415

Asn Tyr Leu Thr Glu Ala Leu Lys Gly Met Asp Lys Met Phe Leu Asn
420 425 430

Asn Thr Thr Asn Arg His Thr Ser Gly Glu Gly Pro Gly Ser Lys
435 440 445

Thr Gly Asp Lys Glu Glu Lys His Arg Lys
450 455

<210> 109

<211> 469

<212> PRT

<213> Homo sapien

<400> 109

Met His Ser Pro Pro Arg Asp Gln Ala Ala Ile Met Leu Trp Lys Leu
1 5 10 15

Val Glu Asn Val Lys Tyr Glu Asp Ile Tyr Glu Met Leu Val His Thr
20 25 30

Tyr Ser Ser Met Asp Arg His Asp Gly Val Pro Ser His Ser Ser Arg
35 40 45

Leu Ser Gln Leu Gly Ser Val Ser Gln Gly Pro Tyr Ser Ser Ala Pro
50 55 60

Pro Leu Ser His Thr Pro Ser Ser Asp Phe Gln Pro Pro Tyr Phe Pro
65 70 75 80

Pro Pro Tyr Gln Pro Leu Pro Tyr His Gln Ser Gln Asp Pro Tyr Ser
85 90 95

His Val Asn Asp Pro Tyr Ser Leu Asn Pro Leu His Gln Pro Gln Gln
100 105 110

98

His Pro Trp Gly Gln Arg Gln Arg Gln Glu Val Gly Ser Glu Ala Gly
115 120 125

Ser Leu Leu Pro Gln Pro Arg Ala Ala Leu Pro Gln Leu Ser Gly Leu
130 135 140

Asp Pro Arg Arg Asp Tyr His Ser Val Arg Arg Pro Asp Val Leu Leu
145 150 155 160

His Ser Ala His His Gly Leu Asp Ala Gly Met Gly Asp Ser Leu Ser
165 170 175

Leu His Gly Leu Gly His Pro Gly Met Glu Asp Val Gln Ser Val Glu
180 185 190

Asp Ala Asn Asn Ser Gly Met Asn Leu Leu Asp Gln Ser Val Ile Lys
195 200 205

Lys Val Pro Val Pro Pro Lys Ser Val Thr Ser Leu Met Met Asn Lys
210 215 220

Asp Gly Phe Leu Gly Gly Met Ser Val Asn Thr Gly Glu Val Phe Cys
225 230 235 240

Ser Val Pro Gly Arg Leu Ser Leu Leu Ser Ser Thr Ser Lys Tyr Lys
245 250 255

Val Thr Val Gly Glu Val Gln Arg Arg Leu Ser Pro Pro Glu Cys Leu
260 265 270

Asn Ala Ser Leu Leu Gly Gly Val Leu Arg Arg Ala Lys Ser Lys Asn
275 280 285

Gly Gly Arg Ser Leu Arg Glu Arg Leu Glu Lys Ile Gly Leu Asn Leu
290 295 300

Pro Ala Gly Arg Arg Lys Ala Ala Asn Val Thr Leu Leu Thr Ser Leu
305 310 315 320

Val Glu Gly Glu Ala Val His Leu Ala Arg Asp Phe Gly Tyr Ile Cys
325 330 335

Glu Thr Glu Phe Pro Ala Lys Ala Val Ser Glu Tyr Leu Asn Arg Gln
340 345 350

His Thr Asp Pro Ser Asp Leu His Ser Arg Lys Asn Met Leu Leu Ala

99

355

360

365

Thr Lys Gln Leu Cys Lys Glu Phe Thr Asp Leu Leu Ala Gln Asp Arg
370 375 380

Thr Pro Ile Gly Asn Ser Arg Pro Ser Pro Ile Leu Glu Pro Gly Ile
385 390 395 400

Gln Ser Cys Leu Thr His Phe Ser Leu Ile Thr His Gly Phe Gly Ala
405 410 415

Pro Ala Ile Cys Ala Ala Leu Thr Ala Leu Gln Asn Tyr Leu Thr Glu
420 425 430

Ala Leu Lys Gly Met Asp Lys Met Phe Leu Asn Asn Thr Thr Thr Asn
435 440 445

Arg His Thr Ser Gly Glu Gly Pro Gly Ser Lys Thr Gly Asp Lys Glu
450 455 460

Glu Lys His Arg Lys
465

<210> 110
<211> 201
<212> PRT
<213> Homo sapien

<400> 110

Met Ala His Ala Met Glu Asn Ser Trp Thr Ile Ser Lys Glu Tyr His
1 5 10 15

Ile Asp Glu Glu Val Gly Phe Ala Leu Pro Asn Pro Gln Glu Asn Leu
20 25 30

Pro Asp Phe Tyr Asn Asp Trp Met Phe Ile Ala Lys His Leu Pro Asp
35 40 45

Leu Ile Glu Ser Gly Gln Leu Arg Glu Arg Val Glu Lys Leu Asn Met
50 55 60

Leu Ser Ile Asp His Leu Thr Asp His Lys Ser Gln Arg Leu Ala Arg
65 70 75 80

Leu Val Leu Gly Cys Ile Thr Met Ala Tyr Val Trp Gly Lys Gly His
85 90 95

100

Gly Asp Val Arg Lys Val Leu Pro Arg Asn Ile Ala Val Pro Tyr Cys
100 105 110

Gln Leu Ser Lys Lys Leu Glu Leu Pro Pro Ile Leu Val Tyr Ala Asp
115 120 125

Cys Val Leu Ala Asn Trp Lys Lys Lys Asp Pro Asn Lys Pro Leu Thr
130 135 140

Tyr Glu Asn Met Asp Val Leu Phe Ser Phe Arg Asp Gly Asp Cys Ser
145 150 155 160

Lys Gly Phe Phe Leu Val Ser Leu Leu Val Glu Ile Ala Ala Ser
165 170 175

Ala Ile Lys Val Arg Leu Ser Ser Leu Gln Asn Leu Tyr Val Asn Leu
180 185 190

Arg Lys Gln Ser Asn His Phe Gly Ala
195 200

<210> 111
<211> 133
<212> PRT
<213> Homo sapien

<400> 111

Met Asp Arg His Ser Ser Tyr Ile Phe Ile Trp Leu Gln Leu Glu Leu
1 5 10 15

Cys Ala Met Ala Val Leu Leu Thr Lys Gly Glu Ile Arg Cys Tyr Cys
20 25 30

Asp Ala Ala His Cys Val Ala Thr Gly Tyr Met Cys Lys Ser Glu Leu
35 40 45

Ser Ala Cys Phe Ser Arg Leu Leu Asp Pro Gln Asn Ser Asn Ser Pro
50 55 60

Leu Thr His Gly Cys Leu Asp Ser Leu Ala Ser Thr Thr Asp Ile Cys
65 70 75 80

Gln Ala Lys Gln Ala Arg Asn His Ser Gly Thr Thr Ile Pro Thr Leu
85 90 95

Glu Cys Cys His Glu Asp Met Cys Asn Tyr Arg Gly Leu His Asp Val

101

100

105

110

Leu Ser Pro Pro Arg Gly Glu Ala Ser Gly Arg Trp Lys Pro Phe Leu
115 120 125

Thr Arg Met Pro Ala
130

<210> 112
<211> 157
<212> PRT
<213> Homo sapien

<400> 112

Ile Ser Leu Gly Gly Val Ser Met Glu Phe Asp His Phe Leu Cys Thr
1 5 10 15

Pro Leu Gly Gln Gly Asn Arg Tyr Gln His Asp Gly Ser Arg Asn Leu
20 25 30

Ile Thr Lys Val Gln Glu Leu Thr Ser Ser Lys Glu Leu Trp Phe Arg
35 40 45

Ala Ala Val Ile Ala Val Pro Ile Ala Gly Gly Leu Ile Leu Val Leu
50 55 60

Leu Ile Met Leu Ala Leu Arg Met Leu Arg Ser Glu Asn Lys Arg Leu
65 70 75 80

Gln Asp Gln Arg Gln Gln Met Leu Ser Arg Leu His Tyr Ser Phe His
85 90 95

Gly His His Ser Lys Lys Gly Gln Val Ala Lys Leu Asp Leu Glu Cys
100 105 110

Met Val Pro Val Ser Gly His Glu Asn Cys Cys Leu Thr Cys Asp Lys
115 120 125

Met Arg Gln Ala Asp Leu Ser Asn Asp Lys Ile Leu Ser Leu Val His
130 135 140

Trp Gly Met Tyr Ser Gly His Gly Lys Leu Glu Phe Val
145 150 155

<210> 113
<211> 121
<212> PRT

102

<213> Homo sapien

<400> 113

Met Asp Arg His Ser Ser Tyr Ile Phe Ile Trp Leu Gln Leu Glu Leu
1 5 10 15

Cys Ala Met Ala Val Leu Leu Thr Lys Gly Glu Ile Arg Cys Tyr Cys
20 25 30

Asp Ala Ala His Cys Val Ala Thr Gly Tyr Met Cys Lys Ser Glu Leu
35 40 45

Ser Ala Cys Phe Ser Arg Leu Leu Asp Pro Gln Asn Ser Asn Ser Pro
50 55 60

Leu Thr His Gly Cys Leu Asp Ser Leu Ala Ser Thr Thr Asp Ile Cys
65 70 75 80

Gln Ala Lys Gln Ala Arg Asn His Ser Gly Thr Thr Ile Pro Thr Leu
85 90 95

Glu Cys Cys His Glu Asp Lys Glu Thr Gly Ile Ser Met Met Val Ala
100 105 110

Glu Thr Leu Ser Pro Arg Cys Arg Ser
115 120

<210> 114

<211> 149

<212> PRT

<213> Homo sapien

<400> 114

Met Arg Leu Met Glu Gly Asp Val Asn Ser Thr Glu Val Leu Ile Ser
1 5 10 15

Ala Arg Ser Tyr Leu Cys Thr Leu Pro Pro Ala Leu Leu Ser Arg Glu
20 25 30

Ile Leu Met Ala Asp Ser Glu Ala Leu Pro Ser Leu Ala Gly Asp Pro
35 40 45

Val Ala Val Glu Ala Leu Leu Arg Ala Val Phe Gly Val Val Val Asp
50 55 60

Glu Ala Ile Gln Lys Gly Thr Ser Val Ser Gln Lys Val Cys Glu Trp
65 70 75 80

103

Lys Glu Pro Glu Glu Leu Lys Gln Leu Leu Asp Leu Glu Leu Arg Ser
85 90 95

Gln Gly Glu Ser Gln Lys Gln Ile Leu Glu Arg Cys Arg Ala Val Ile
100 105 110

Arg Tyr Ser Val Lys Thr Gly His Pro Arg Phe Phe Asn Gln Leu Phe
115 120 125

Ser Gly Leu Asp Pro His Ala Leu Ala Gly Arg Ile Ile Thr Glu Ser
130 135 140

Leu Asn Thr Ser Gln
145

<210> 115
<211> 204
<212> PRT
<213> Homo sapien

<400> 115

Gly Pro Val Trp Ala Val Pro Pro His Leu Ser Phe Leu Val Val Leu
1 5 10 15

Ser Pro Gly Arg Tyr Thr Tyr Glu Ile Ala Pro Val Phe Val Leu Met
20 25 30

Glu Glu Glu Val Leu Arg Lys Leu Arg Ala Leu Val Gly Trp Ser Ser
35 40 45

Gly Asp Gly Ile Phe Cys Pro Gly Gly Ser Ile Ser Asn Met Tyr Ala
50 55 60

Val Asn Leu Ala Arg Tyr Gln Arg Tyr Pro Asp Cys Lys Gln Arg Gly
65 70 75 80

Leu Arg Thr Leu Pro Pro Leu Ala Leu Phe Thr Ser Lys Glu Val Gly
85 90 95

Lys Arg His Arg Pro Asn Pro Gly Leu Leu Ile Leu Ile Ser Ser Gln
100 105 110

Leu Ser Arg Asp Leu Pro Gly Leu Leu Pro Ala Leu Pro Thr Ser Ser
115 120 125

104

Lys Ala Ser Leu Pro Pro Gly Gly Cys Ala Ser Phe Gln Ser Arg Arg
130 135 140

Ser Ser Asn Cys Ser Cys Ser His Cys Leu Leu Phe Gly Gly Arg Gly
145 150 155 160

Gly Ala Val Ser Ala Val Asp Thr Val His Thr Leu Pro Thr Gln Glu
165 170 175

Cys Gly Leu Trp Thr Ser Ser Ile Gly Met Thr Trp Gly Leu Leu Glu
180 185 190

Met Gln Asn Leu Ala Gly His Gly Asp Ser Arg Leu
195 200

<210> 116
<211> 194
<212> PRT
<213> Homo sapien

<400> 116

Met Gln Arg Pro Gly Trp Trp Lys Gly Glu Glu Asn Trp Ala Gly Gln
1 5 10 15

Ile Ser Gly Trp Gly Leu Trp Arg Trp Arg Gly Gln Gly Trp Ser Pro
20 25 30

Gly Thr Lys Lys Gly Arg Gly Ser Ala Arg Pro Glu Glu Trp Glu Glu
35 40 45

Met Gly Pro Gly Cys Arg Val Pro Arg Gly Leu Gly Gln Gly Pro Arg
50 55 60

Cys Arg Arg Lys Met Arg Glu Phe Gly Phe Gly Asp Leu Val His Pro
65 70 75 80

Gly Pro Val Leu Pro Pro Leu Pro Pro Gln Arg Arg Ala Ser Cys Ile
85 90 95

Pro Phe Leu Trp Pro Glu Gly Ser Ser Val His Pro Ser Gln Ala Leu
100 105 110

Ala Ser Ser His Ser Pro Ala Leu Gly Pro Ile Arg Leu Gly Arg Met
115 120 125

Gly Glu Pro Val Val Ala Pro Gly Arg Gly Lys Gly Gly Arg Leu Gly
130 135 140

105

Lys Pro Leu Leu Gly Arg Thr Gln Tyr Ser Gly Ser Ser Leu Ser Gly
145 150 155 160

Lys Glu Arg Ile Cys Val Thr Arg Ser Tyr Arg Gly Thr Leu Arg Gly
165 170 175

Leu Arg Gly Arg Ala Trp Ser Pro Pro Arg Gly Lys Glu Lys Phe Phe
180 185 190

Glu Ser

<210> 117

<211> 472

<212> PRT

<213> Homo sapien

<400> 117

Met Ser Asp Thr Ser Glu Ser Gly Ala Gly Leu Thr Arg Phe Gln Ala
1 5 10 15

Glu Ala Ser Glu Lys Asp Ser Ser Ser Met Met Gln Thr Leu Leu Thr
20 25 30

Val Thr Gln Asn Val Glu Val Pro Glu Thr Pro Lys Ala Ser Lys Ala
35 40 45

Leu Glu Val Ser Glu Asp Val Lys Val Ser Lys Ala Ser Gly Val Ser
50 55 60

Lys Ala Thr Glu Val Ser Lys Thr Pro Glu Ala Arg Glu Ala Pro Ala
65 70 75 80

Thr Gln Ala Ser Ser Thr Thr Gln Leu Thr Asp Thr Gln Val Leu Ala
85 90 95

Ala Glu Asn Lys Ser Leu Ala Ala Asp Thr Lys Lys Gln Asn Ala Asp
100 105 110

Pro Gln Ala Val Thr Met Pro Ala Thr Glu Thr Lys Lys Val Ser His
115 120 125

Val Ala Asp Thr Lys Val Asn Thr Lys Ala Gln Glu Thr Glu Ala Ala
130 135 140

106

Pro Ser Gln Ala Pro Ala Asp Glu Pro Glu Pro Glu Ser Ala Ala Ala
145 150 155 160

Gln Ser Gln Glu Asn Gln Asp Thr Arg Pro Lys Val Lys Ala Lys Lys
165 170 175

Ala Arg Lys Val Lys His Leu Asp Gly Glu Glu Asp Gly Ser Ser Asp
180 185 190

Gln Ser Gln Ala Ser Gly Thr Thr Gly Gly Arg Arg Val Ser Lys Ala
195 200 205

Leu Met Ala Ser Met Ala Arg Arg Ala Ser Arg Gly Pro Ile Ala Phe
210 215 220

Trp Ala Arg Arg Ala Ser Arg Thr Arg Leu Ala Ala Trp Ala Arg Arg
225 230 235 240

Ala Leu Leu Ser Leu Arg Ser Pro Lys Ala Arg Arg Gly Lys Ala Arg
245 250 255

Arg Arg Ala Ala Lys Leu Gln Ser Ser Gln Glu Pro Glu Ala Pro Pro
260 265 270

Pro Arg Asp Val Ala Leu Leu Gln Gly Arg Ala Asn Asp Leu Val Lys
275 280 285

Tyr Leu Leu Ala Lys Asp Gln Thr Lys Ile Pro Ile Lys Arg Ser Asp
290 295 300

Met Leu Lys Asp Ile Ile Lys Glu Tyr Thr Asp Val Tyr Pro Glu Ile
305 310 315 320

Ile Glu Arg Ala Gly Tyr Ser Leu Glu Lys Val Phe Gly Ile Gln Leu
325 330 335

Lys Glu Ile Asp Lys Asn Asp His Leu Tyr Ile Leu Leu Ser Thr Leu
340 345 350

Glu Pro Thr Asp Ala Gly Ile Leu Gly Thr Thr Lys Asp Ser Pro Lys
355 360 365

Leu Gly Leu Leu Met Val Leu Leu Ser Ile Ile Phe Met Asn Gly Asn
370 375 380

Arg Ser Ser Glu Gly Glu Trp Leu Gly Leu Gln Leu Asn Gly Trp Leu

107

385

390

395

400

Trp Ser Arg Phe His Val Phe Asn Phe Cys Pro Cys Leu Leu Leu Pro
405 410 415

Pro Leu Ala Ala Val Ile Trp Glu Val Leu Arg Lys Leu Gly Leu Arg
420 425 430

Pro Gly Tyr Asp Trp Ala Leu Ser Ala Leu Ala Val Arg Val Val Leu
435 440 445

Trp Gln Glu Arg Thr Val Leu Gly Leu His Gln Ser Gly Gly Leu Val
450 455 460

Glu Arg Val Gly Cys Trp Thr Gly
465 470

<210> 118
<211> 528
<212> PRT
<213> Homo sapien

<400> 118

Met Ser Asp Thr Ser Glu Ser Gly Ala Gly Leu Thr Arg Phe Gln Ala
1 5 10 15

Glu Ala Ser Glu Lys Asp Ser Ser Met Met Gln Thr Leu Leu Thr
20 25 30

Val Thr Gln Asn Val Glu Val Pro Glu Thr Pro Lys Ala Ser Lys Ala
35 40 45

Leu Glu Val Ser Glu Asp Val Lys Val Ser Lys Ala Ser Gly Val Ser
50 55 60

Lys Ala Thr Glu Val Ser Lys Thr Pro Glu Ala Arg Glu Ala Pro Ala
65 70 75 80

Thr Gln Ala Ser Ser Thr Thr Gln Leu Thr Asp Thr Gln Val Leu Ala
85 90 95

Ala Glu Asn Lys Ser Leu Ala Ala Asp Thr Lys Lys Gln Asn Ala Asp
100 105 110

Pro Gln Ala Val Thr Met Pro Ala Thr Glu Thr Lys Lys Val Ser His
115 120 125

108

Val Ala Asp Thr Lys Val Asn Thr Lys Ala Gln Glu Thr Glu Ala Ala
130 135 140

Pro Ser Gln Ala Pro Ala Asp Glu Pro Glu Pro Glu Ser Ala Ala Ala
145 150 155 160

Gln Ser Gln Glu Asn Gln Asp Thr Arg Pro Lys Val Lys Ala Lys Lys
165 170 175

Ala Arg Lys Val Lys His Leu Asp Gly Glu Glu Asp Gly Ser Ser Asp
180 185 190

Gln Ser Gln Ala Ser Gly Thr Thr Gly Gly Arg Arg Val Ser Lys Ala
195 200 205

Leu Met Ala Ser Met Ala Arg Arg Ala Ser Arg Gly Pro Ile Ala Phe
210 215 220

Trp Ala Arg Arg Ala Ser Arg Thr Arg Leu Ala Ala Trp Ala Arg Arg
225 230 235 240

Ala Leu Leu Ser Leu Arg Ser Pro Lys Ala Arg Arg Gly Lys Ala Arg
245 250 255

Arg Arg Ala Ala Lys Leu Gln Ser Ser Gln Glu Pro Glu Ala Pro Pro
260 265 270

Pro Arg Asp Val Ala Leu Leu Gln Gly Arg Ala Asn Asp Leu Val Lys
275 280 285

Tyr Leu Leu Ala Lys Asp Gln Thr Lys Ile Pro Ile Lys Arg Ser Gly
290 295 300

Lys Val Leu Thr Asn Pro Pro Ser Ala Leu Ser Ser Ala Leu His Cys
305 310 315 320

Pro Tyr Thr Ile Val Leu Gly Ile Ser Pro Ala Leu Met Leu Met Ser
325 330 335

Leu Ser Ser Gln Ser Ser Asp Leu Ala Val Leu Ala Ser Leu Leu Ile
340 345 350

Ser Thr Glu Pro Gly Tyr Ala Thr Leu Gly Val Val Gly Lys Glu Ser
355 360 365

109

Ile Ala Trp Ala Ser Gly Pro Pro Gly Ile Ser Ser Val Arg Cys Ser
370 375 380

Gln His Ser Pro Leu Ala Asp Met Leu Lys Asp Ile Ile Lys Glu Tyr
385 390 395 400

Thr Asp Val Tyr Pro Glu Ile Ile Glu Arg Ala Gly Tyr Ser Leu Glu
405 410 415

Lys Val Phe Gly Ile Gln Leu Lys Glu Ile Asp Lys Asn Asp His Leu
420 425 430

Tyr Ile Leu Leu Ser Thr Leu Glu Pro Thr Asp Ala Gly Ile Leu Gly
435 440 445

Thr Thr Lys Asp Ser Pro Lys Leu Gly Leu Leu Met Val Leu Leu Ser
450 455 460

Ile Ile Phe Met Asn Gly Asn Arg Ser Ser Glu Ala Val Ile Trp Glu
465 470 475 480

Val Leu Arg Lys Leu Gly Leu Arg Pro Gly Tyr Asp Trp Ala Leu Ser
485 490 495

Ala Leu Ala Val Arg Val Val Leu Trp Gln Glu Arg Thr Val Leu Gly
500 505 510

Leu His Gln Ser Gly Gly Leu Val Glu Arg Val Gly Cys Trp Thr Gly
515 520 525

<210> 119
<211> 314
<212> PRT
<213> Homo sapien

<400> 119

Asp Met Ser Asp Thr Ser Glu Ser Gly Ala Gly Leu Thr Arg Phe Gln
1 5 10 15

Ala Glu Ala Ser Glu Lys Asp Ser Ser Ser Met Met Gln Thr Leu Leu
20 25 30

Thr Val Thr Gln Asn Val Glu Val Pro Glu Thr Pro Lys Ala Ser Lys
35 40 45

Ala Leu Glu Val Ser Glu Asp Val Lys Val Ser Lys Ala Ser Gly Val
50 55 60

110

Ser Lys Ala Thr Glu Val Ser Lys Thr Pro Glu Ala Arg Glu Ala Pro
65 70 75 80

Ala Thr Gln Ala Ser Ser Thr Thr Gln Leu Thr Asp Thr Gln Val Leu
85 90 95

Ala Ala Glu Asn Lys Ser Leu Ala Ala Asp Thr Lys Lys Gln Asn Ala
100 105 110

Asp Pro Gln Ala Val Thr Met Pro Ala Thr Glu Thr Lys Lys Val Ser
115 120 125

His Val Ala Asp Thr Lys Val Asn Thr Lys Ala Gln Glu Thr Glu Ala
130 135 140

Ala Pro Ser Gln Ala Pro Ala Asp Glu Pro Glu Pro Glu Ser Ala Ala
145 150 155 160

Ala Gln Ser Gln Glu Asn Gln Asp Thr Arg Pro Lys Val Lys Ala Lys
165 170 175

Lys Ala Arg Lys Val Lys His Leu Asp Gly Glu Glu Asp Gly Ser Ser
180 185 190

Asp Gln Ser Gln Ala Ser Gly Thr Thr Gly Gly Arg Arg Val Ser Lys
195 200 205

Ala Leu Met Ala Ser Met Ala Arg Arg Ala Ser Arg Gly Pro Ile Ala
210 215 220

Phe Trp Ala Arg Arg Ala Ser Arg Thr Arg Leu Ala Ala Trp Ala Arg
225 230 235 240

Arg Ala Leu Leu Ser Leu Arg Ser Pro Lys Ala Arg Arg Gly Lys Ala
245 250 255

Arg Arg Arg Ala Ala Lys Leu Gln Ser Ser Gln Glu Pro Glu Ala Pro
260 265 270

Pro Pro Arg Asp Val Ala Leu Leu Gln Gly Arg Ala Asn Asp Leu Val
275 280 285

Lys Tyr Leu Leu Ala Lys Asp Gln Thr Lys Ile Pro Ile Lys Arg Ser
290 295 300

111

Gly Lys Val Leu Pro Ile Leu Pro Leu Pro
305 310

<210> 120
<211> 35
<212> PRT
<213> Homo sapien

<400> 120

Ala Leu Thr Ala Leu Pro Gly Ala Ala Gly Ala Arg Arg Arg His Asp
1 5 10 15

Pro Leu Arg Leu Arg Gly Arg Arg Ala His Arg Glu Lys Ala Arg Gln
- 20 25 30

Gly Ser Ala
35

<210> 121
<211> 80
<212> PRT
<213> Homo sapien

<400> 121

Gly Arg Arg Ile Phe Glu Arg Thr Leu Gln Ile Leu Arg Thr Ser Val
1 5 10 15

Ala Leu Glu Thr Val Ser Trp Ile Ser Ile Phe Leu Cys Glu Gly Leu
20 25 30

Leu Leu Met Ser Pro Arg Ile Gln Thr Gln Thr Tyr Phe Ser Lys Lys
35 40 45

Val Gln Leu Gly Cys Tyr Ile Val Ala Arg Val Tyr Leu His Ala His
50 55 60

Leu Ala Phe Gln Ala Pro Ile Thr Ser Lys Val Ser Leu Lys Leu Phe
65 70 75 80

<210> 122
<211> 33
<212> PRT
<213> Homo sapien

<400> 122

Ala Leu Thr Ala Leu Pro Gly Ala Ala Gly Ala Arg Arg Arg His Asp
1 5 10 15

112

Pro Leu Arg Leu Arg Gly Arg Arg Ala His Arg Glu Lys Lys Pro Thr
20 25 30

Gly

<210> 123
<211> 80
<212> PRT
<213> Homo sapien

<400> 123

Gly Arg Arg Ile Phe Glu Arg Thr Leu Gln Ile Leu Arg Thr Ser Val
1 5 10 15

Ala Leu Glu Thr Val Ser Trp Ile Ser Ile Phe Leu Cys Glu Gly Leu
20 25 30

Leu Leu Met Ser Pro Arg Ile Gln Thr Gln Thr Tyr Phe Ser Lys Lys
35 40 45

Val Gln Leu Gly Cys Tyr Ile Val Ala Arg Val Tyr Leu His Ala His
50 55 60

Leu Ala Phe Gln Ala Pro Ile Thr Ser Lys Val Ser Leu Lys Leu Phe
65 70 75 80

<210> 124
<211> 73
<212> PRT
<213> Homo sapien

<400> 124

Met Ala Ile Arg Glu Leu Lys Val Cys Leu Leu Gly Asp Thr Gly Val
1 5 10 15

Gly Lys Ser Ser Ile Val Cys Arg Phe Val Gln Asp His Phe Asp His
20 25 30

Asn Ile Ser Pro Thr Ile Gly Ala Ser Phe Met Thr Lys Thr Val Pro
35 40 45

Cys Gly Asn Glu Leu His Lys Phe Leu Ile Trp Asp Thr Ala Gly Gln
50 55 60

Glu Arg Gly Gly Ser Pro Glu Gly Cys
65 70

<210> 125
<211> 94
<212> PRT
<213> Homo sapien

<400> 125

Thr Val Phe Arg Pro Thr Gly Tyr Leu Ala Tyr Cys Phe Asn Ile Ile
1 5 10 15

Val Glu Thr Arg Pro Cys Ser Pro Val Val Leu Pro Cys Cys Ala Asn
20 25 30

Cys Ser Phe Phe Ser Cys Phe Cys Lys Glu Leu Pro Ser Gly Leu Asp
35 40 45

Pro Val Leu Ala His Thr Arg His Arg Cys Ser Gln Leu Gly Pro Phe
50 55 60

Arg His Val Phe Tyr Ser Val Val Lys His Phe His Gln Gln Cys Leu
65 70 75 80

Ile Val Ser Val Ile Phe Gly Leu Thr His Thr Asp Ser Tyr
85 90

<210> 126
<211> 54
<212> PRT
<213> Homo sapien

<400> 126

Val Asp Asp Arg Cys Leu Val Thr Leu Gly Asn Arg Cys Cys Ala Ala
1 5 10 15

Lys Glu Trp Thr Val Arg Gly Arg Gln Ile Pro Pro Leu Asp Pro His
20 25 30

Glu Asn Gly Asn Asn Gly Thr Ile Lys Val Glu Lys Pro Thr Met Gln
35 40 45

Ala Ser Arg Arg Cys Cys
50

<210> 127
<211> 94
<212> PRT
<213> Homo sapien

114

<400> 127

Thr Val Phe Arg Pro Thr Gly Tyr Leu Ala Tyr Cys Phe Asn Ile Ile
1 5 10 15

Val Glu Thr Arg Pro Cys Ser Pro Val Val Leu Pro Cys Cys Ala Asn
20 25 30

Cys Ser Phe Phe Ser Cys Phe Cys Lys Glu Leu Pro Ser Gly Leu Asp
35 40 45

Pro Val Leu Ala His Thr Arg His Arg Cys Ser Gln Leu Gly Pro Phe
50 55 60

Arg His Val Phe Tyr Ser Val Val Lys His Phe His Gln Gln Cys Leu
65 70 75 80

Ile Val Ser Val Ile Phe Gly Leu Thr His Thr Asp Ser Tyr
85 90

<210> 128

<211> 284

<212> PRT

<213> Homo sapien

<400> 128

Met Gly Trp Ser Gly Arg Ser Gly Lys Gly Lys Leu Arg Arg Arg Ser
1 5 10 15

Val Ser Gly Asn Met Ala Ser Arg Ser Lys Arg Arg Ala Val Glu Ser
20 25 30

Gly Val Pro Gln Pro Pro Asp Pro Pro Val Gln Arg Asp Glu Glu Glu
35 40 45

Glu Lys Glu Val Glu Asn Glu Asp Glu Asp Asp Asp Ser Asp Lys
50 55 60

Glu Lys Asp Glu Glu Asp Glu Val Ile Asp Glu Glu Val Asn Ile Glu
65 70 75 80

Phe Glu Ala Tyr Ser Leu Ser Asp Asn Asp Tyr Asp Gly Ile Lys Lys
85 90 95

Leu Leu Gln Gln Leu Phe Leu Lys Ala Pro Val Asn Thr Ala Glu Leu
100 105 110

115

Thr Asp Leu Leu Ile Gln Gln Asn His Ile Gly Ser Val Ile Lys Gln
115 120 125

Thr Asp Val Ser Glu Asp Ser Asn Asp Asp Met Asp Glu Asp Glu Val
130 135 140

Phe Gly Phe Ile Ser Leu Leu Asn Leu Thr Glu Arg Lys Gly Thr Gln
145 150 155 160

Cys Val Glu Gln Ile Gln Glu Leu Val Leu Arg Phe Cys Glu Lys Asn
165 170 175

Cys Glu Lys Ser Met Val Glu Gln Leu Asp Lys Phe Leu Asn Asp Thr
180 185 190

Thr Lys Pro Val Gly Leu Leu Leu Ser Glu Arg Phe Ile Asn Val Pro
195 200 205

Pro Gln Ile Ala Leu Pro Met Tyr Gln Gln Leu Gln Lys Glu Leu Ala
210 215 220

Gly Ala His Arg Thr Asn Lys Pro Cys Gly Lys Cys Tyr Phe Tyr Leu
225 230 235 240

Leu Ile Ser Lys Thr Phe Val Glu Ala Gly Lys Asn Asn Ser Lys Lys
245 250 255

Lys Pro Ser Asn Lys Lys Ala Ala Leu Met Phe Ala Asn Ala Glu
260 265 270

Glu Glu Phe Phe Tyr Glu Val Val His Gly Gly Lys
275 280

<210> 129
<211> 220
<212> PRT
<213> Homo sapien

<400> 129

Met Gly Trp Ser Gly Arg Ser Gly Lys Gly Lys Leu Arg Arg Arg Ser
1 5 10 15

Val Ser Gly Asn Met Ala Ser Arg Ser Lys Arg Arg Ala Val Glu Ser
20 25 30

Gly Val Pro Gln Pro Pro Asp Pro Pro Val Gln Arg Asp Glu Glu Glu
35 40 45

Glu Lys Glu Val Glu Asn Glu Asp Glu Asp Asp Asp Asp Ser Asp Lys
50 55 60

Glu Lys Asp Glu Glu Asp Glu Val Ile Asp Glu Glu Val Asn Ile Glu
65 70 75 80

Phe Glu Ala Tyr Ser Leu Ser Asp Asn Asp Tyr Asp Gly Ile Lys Lys
85 90 95

Leu Leu Gln Gln Leu Phe Leu Lys Ala Pro Val Asn Thr Ala Glu Leu
100 105 110

Thr Asp Leu Leu Ile Gln Gln Asn His Ile Gly Ser Val Ile Lys Gln
115 120 125

Thr Asp Val Ser Glu Asp Ser Asn Asp Asp Met Asp Glu Asp Glu Val
130 135 140

Phe Gly Phe Ile Ser Leu Leu Asn Leu Thr Glu Arg Lys Gly Thr Gln
145 150 155 160

Cys Val Glu Gln Ile Gln Glu Leu Val Leu Arg Phe Cys Glu Lys Asn
165 170 175

Cys Glu Lys Ser Met Val Glu Gln Leu Asp Lys Phe Leu Asn Asp Thr
180 185 190

Thr Lys Pro Val Gly Leu Leu Ser Glu Arg Phe Ile Asn Val Pro
195 200 205

Pro Gln Ile Ala Leu Pro Met Tyr Gln Gln Leu Gln
210 215 220

<210> 130
<211> 190
<212> PRT
<213> Homo sapien

<400> 130

Met Gly Trp Ser Gly Arg Ser Gly Lys Gly Lys Leu Arg Arg Arg Ser
1 5 10 15

Val Ser Gly Asn Met Ala Ser Arg Ser Lys Arg Arg Ala Val Glu Ser
20 25 30

117

Gly Val Pro Gln Pro Pro Asp Pro Pro Val Gln Arg Asp Glu Glu Glu
35 40 45

Glu Lys Glu Val Glu Asn Glu Asp Glu Asp Asp Asp Ser Asp Lys
50 55 60

Glu Lys Asp Glu Glu Asp Glu Val Ile Asp Glu Glu Val Asn Ile Glu
65 70 75 80

Phe Glu Ala Tyr Ser Leu Ser Asp Asn Asp Tyr Asp Gly Ile Lys Lys
85 90 95

Leu Leu Gln Gln Leu Phe Leu Lys Ala Pro Val Asn Thr Ala Glu Leu
100 105 110

Thr Asp Leu Leu Ile Gln Gln Asn His Ile Gly Ser Val Ile Lys Gly
115 120 125

Thr Gln Cys Val Glu Gln Ile Gln Glu Leu Val Leu Arg Phe Cys Glu
130 135 140

Lys Asn Cys Glu Lys Ser Met Val Glu Gln Leu Asp Lys Phe Leu Asn
145 150 155 160

Asp Thr Thr Lys Pro Val Gly Leu Leu Ser Glu Arg Phe Ile Asn
165 170 175

Val Pro Pro Gln Ile Ala Leu Pro Met Tyr Gln Gln Leu Gln
180 185 190

<210> 131
<211> 305
<212> PRT
<213> Homo sapien

<400> 131

Met Ala Ser Arg Lys Glu Asn Ala Lys Ser Ala Asn Arg Val Leu Arg
1 5 10 15

Ile Ser Gln Leu Asp Ala Leu Glu Leu Asn Lys Ala Leu Glu Gln Leu
20 25 30

Val Trp Ser Gln Phe Thr Gln Cys Phe His Gly Phe Lys Pro Gly Leu
35 40 45

Leu Ala Arg Phe Glu Pro Glu Val Lys Ala Cys Leu Trp Val Phe Leu
50 55 60

Trp Arg Phe Thr Ile Tyr Ser Lys Asn Ala Thr Val Gly Gln Ser Val
65 70 75 80

Leu Asn Ile Lys Tyr Lys Asn Asp Phe Ser Pro Asn Leu Arg Tyr Gln
85 90 95

Pro Pro Ser Lys Asn Gln Lys Ile Trp Tyr Ala Val Cys Thr Ile Gly
100 105 110

Gly Arg Trp Leu Glu Glu Arg Cys Tyr Asp Leu Phe Arg Asn His His
115 120 125

Leu Ala Ser Phe Gly Lys Val Lys Gln Cys Val Asn Phe Val Ile Gly
130 135 140

Leu Leu Lys Leu Gly Gly Leu Ile Asn Phe Leu Ile Phe Leu Gln Arg
145 150 155 160

Gly Lys Phe Ala Thr Leu Thr Glu Arg Leu Leu Gly Ile His Ser Val
165 170 175

Phe Cys Lys Pro Gln Asn Ile Arg Glu Val Gly Phe Glu Tyr Met Asn
180 185 190

Arg Glu Leu Leu Trp His Gly Phe Ala Glu Phe Leu Ile Phe Leu Leu
195 200 205

Pro Leu Ile Asn Val Gln Lys Leu Lys Ala Lys Leu Ser Ser Trp Cys
210 215 220

Ile Pro Leu Thr Gly Ala Pro Asn Ser Asp Asn Thr Leu Ala Thr Ser
225 230 235 240

Gly Lys Glu Cys Ala Leu Cys Gly Glu Trp Pro Thr Met Pro His Thr
245 250 255

Ile Gly Cys Glu His Ile Phe Cys Tyr Phe Cys Ala Lys Ser Ser Phe
260 265 270

Leu Phe Asp Val Tyr Phe Thr Cys Pro Lys Cys Gly Thr Glu Val His
275 280 285

Ser Leu Gln Pro Leu Lys Ser Gly Ile Glu Met Ser Glu Val Asn Ala
290 295 300

Leu
305

<210> 132
<211> 582
<212> PRT
<213> Homo sapien

<400> 132

Met Ala Ala Arg Ser Trp Gln Asp Glu Leu Ala Gln Gln Ala Glu Glu
1 5 10 15

Gly Ser Ala Arg Leu Arg Glu Met Leu Ser Val Gly Leu Gly Phe Leu
20 25 30

Arg Thr Glu Leu Gly Leu Asp Leu Gly Leu Glu Pro Lys Arg Tyr Pro
35 40 45

Gly Trp Val Ile Leu Val Gly Thr Gly Ala Leu Gly Leu Leu Leu Leu
50 55 60

Phe Leu Leu Gly Tyr Gly Trp Ala Ala Ala Cys Ala Gly Ala Arg Lys
65 70 75 80

Lys Arg Arg Ser Pro Pro Arg Lys Arg Glu Glu Ala Ala Ala Val Pro
85 90 95

Ala Ala Ala Pro Asp Asp Leu Ala Leu Leu Lys Asn Leu Arg Ser Glu
100 105 110

Glu Gln Lys Lys Lys Asn Arg Lys Lys Leu Ser Glu Lys Pro Lys Pro
115 120 125

Asn Gly Arg Thr Val Glu Val Ala Glu Gly Glu Ala Val Arg Thr Pro
130 135 140

Gln Ser Val Thr Ala Lys Gln Pro Pro Glu Ile Asp Lys Lys Asn Glu
145 150 155 160

Lys Ser Lys Lys Asn Lys Lys Ser Lys Ser Asp Ala Lys Ala Val
165 170 175

Gln Asn Ser Ser Arg His Asp Gly Lys Glu Val Asp Glu Gly Ala Trp
180 185 190

Glu Thr Lys Ile Ser His Arg Glu Lys Arg Gln Gln Arg Lys Arg Asp

120

195	200	205
Lys Val Leu Thr Asp Ser Gly Ser Leu Asp Ser Thr Ile Pro Gly Ile		
210	215	220
Glu Asn Thr Ile Thr Val Thr Thr Glu Gln Leu Thr Thr Ala Ser Phe		
225	230	235
240		
Pro Val Gly Ser Lys Lys Asn Lys Gly Asp Ser His Leu Asn Val Gln		
245	250	255
Val Ser Asn Phe Lys Ser Gly Lys Gly Asp Ser Thr Leu Gln Val Ser		
260	265	270
Ser Gly Leu Asn Glu Asn Leu Thr Val Asn Gly Gly Trp Asn Glu		
275	280	285
Lys Ser Val Lys Leu Ser Ser Gln Ile Ser Ala Gly Glu Glu Lys Trp		
290	295	300
Asn Ser Val Ser Pro Ala Ser Ala Gly Lys Arg Lys Thr Glu Pro Ser		
305	310	320
Ala Trp Ser Gln Asp Thr Gly Asp Ala Asn Thr Asn Gly Lys Asp Trp		
325	330	335
Gly Arg Ser Trp Ser Asp Arg Ser Ile Phe Ser Gly Ile Gly Ser Thr		
340	345	350
Ala Glu Pro Val Ser Gln Ser Thr Thr Ser Asp Tyr Gln Trp Asp Val		
355	360	365
Ser Arg Asn Gln Pro Tyr Ile Asp Asp Glu Trp Ser Gly Leu Asn Gly		
370	375	380
Leu Ser Ser Ala Asp Pro Asn Ser Asp Trp Asn Ala Pro Ala Glu Glu		
385	390	400
Trp Gly Asn Trp Val Asp Glu Glu Arg Ala Ser Leu Leu Lys Ser Gln		
405	410	415
Glu Pro Ile Pro Asp Asp Gln Lys Val Ser Asp Asp Asp Lys Glu Lys		
420	425	430
Gly Glu Gly Ala Leu Pro Thr Gly Lys Ser Lys Lys Lys Lys Lys		
435	440	445

Lys Lys Lys Gln Gly Glu Asp Asn Ser Thr Ala Gln Asp Thr Glu Glu
450 455 460

Leu Glu Lys Glu Ile Arg Glu Asp Leu Pro Val Asn Thr Ser Lys Thr
465 470 475 480

Arg Pro Lys Gln Glu Lys Ala Phe Ser Leu Lys Thr Ile Ser Thr Ser
485 490 495

Asp Pro Ala Glu Val Leu Val Lys Asn Ser Gln Pro Ile Lys Thr Leu
500 505 510

Pro Pro Ala Thr Ser Thr Glu Pro Ser Val Ile Leu Ser Lys Ser Asp
515 520 525

Ser Asp Lys Ser Ser Ser Gln Val Pro Pro Ile Leu Gln Glu Thr Asp
530 535 540

Lys Ser Lys Ser Asn Thr Lys Gln Asn Ser Val Pro Pro Ser Gln Thr
545 550 555 560

Lys Ser Glu Thr Ser Trp Glu Ser Pro Lys Gln Ile Lys Lys Lys Lys
565 570 575

Lys Ala Arg Arg Glu Thr
580

<210> 133
<211> 389
<212> PRT
<213> Homo sapien

<400> 133

Met Asp Ala Trp Ser Arg Pro Arg Tyr Ser Leu Glu Pro Val Ala Val
1 5 10 15

Glu Leu Lys Ser Leu Leu Gly Lys Ser Lys Cys Gln Ala Leu Val Leu
20 25 30

Val Asp Leu Trp Arg Gly Lys Leu Ser Ser Thr Leu Leu Leu Val Phe
35 40 45

Asn Phe His Thr Ala Gln Val Ser Ser Ser Leu Pro Leu Leu Arg Asp
50 55 60

122

Val Leu Phe Leu Lys Asp Cys Val Gly Pro Glu Val Glu Lys Ala Cys
65 70 75 80

Ala Asn Pro Ala Ala Gly Ser Val Ile Leu Leu Glu Asn Leu Arg Phe
85 90 95

His Val Glu Glu Glu Gly Lys Gly Lys Asp Ala Ser Gly Asn Lys Val
100 105 110

Lys Ala Glu Pro Ala Lys Ile Glu Ala Phe Arg Ala Ser Leu Ser Lys
115 120 125

Leu Gly Asp Val Tyr Val Asn Asp Ala Phe Gly Thr Ala His Arg Ala
130 135 140

His Ser Ser Met Val Gly Val Asn Leu Pro Gln Lys Ala Gly Gly Phe
145 150 155 160

Leu Met Lys Lys Glu Leu Asn Tyr Phe Ala Lys Ala Leu Glu Ser Pro
165 170 175

Glu Arg Pro Phe Leu Ala Ile Leu Gly Gly Ala Lys Val Ala Asp Lys
180 185 190

Ile Gln Leu Ile Asn Asn Met Leu Asp Lys Val Asn Glu Met Ile Ile
195 200 205

Gly Gly Gly Met Ala Phe Thr Phe Leu Lys Val Leu Asn Asn Met Glu
210 215 220

Ile Gly Thr Ser Leu Phe Asp Glu Glu Gly Ala Lys Ile Val Lys Asp
225 230 235 240

Leu Met Ser Lys Ala Glu Lys Asn Gly Val Lys Ile Thr Leu Pro Val
245 250 255

Asp Phe Val Thr Ala Asp Lys Phe Asp Glu Asn Ala Lys Thr Gly Gln
260 265 270

Ala Thr Val Ala Ser Gly Ile Pro Ala Gly Trp Met Gly Leu Asp Cys
275 280 285

Gly Pro Glu Ser Ser Lys Lys Tyr Ala Glu Ala Val Thr Arg Ala Lys
290 295 300

Gln Ile Val Trp Asn Gly Pro Val Gly Val Phe Glu Trp Glu Ala Phe

123

305

310

315

320

Ala Arg Gly Thr Lys Ala Leu Met Asp Glu Val Val Lys Ala Thr Ser
325 330 335

Arg Gly Cys Ile Thr Ile Ile Gly Gly Asp Thr Ala Thr Cys Cys
340 345 350

Ala Lys Trp Asn Thr Glu Asp Lys Val Ser His Val Ser Thr Gly Gly
355 360 365

Gly Ala Ser Leu Glu Leu Leu Glu Gly Lys Val Leu Pro Gly Val Asp
370 375 380

Ala Leu Ser Asn Ile
385

<210> 134
<211> 121
<212> PRT
<213> Homo sapien

<400> 134

Met Ala Ser Ser Asp Ile Gln Val Lys Glu Leu Glu Lys Arg Ala Ser
1 5 10 15

Gly Gln Ala Phe Glu Leu Ile Leu Ser Pro Arg Ser Lys Glu Ser Val
20 25 30

Pro Glu Phe Pro Leu Ser Pro Pro Lys Lys Lys Asp Leu Ser Leu Glu
35 40 45

Glu Ile Gln Lys Lys Leu Glu Ala Ala Glu Glu Arg Arg Lys Ser His
50 55 60

Glu Ala Glu Val Leu Lys Gln Leu Ala Glu Lys Arg Glu His Glu Lys
65 70 75 80

Glu Val Leu Gln Lys Ala Ile Glu Glu Asn Asn Asn Phe Ser Lys Met
85 90 95

Ala Glu Glu Lys Leu Thr His Lys Met Glu Ala Lys Val Phe Tyr Ser
100 105 110

Phe Ser Lys Val Leu Val Phe Leu Met
115 120

<210> 135
<211> 121
<212> PRT
<213> Homo sapien

<400> 135

Met Val Ala Ser Ala Glu Met Phe Leu Gly Cys Glu Glu Leu Gly Val
1 5 10 15

Ser Leu Glu Gly Pro Gln Asp Gln Met Thr Cys Glu Glu Tyr Val Ala
20 25 30

Phe Ile Leu Ala Ala Gly Glu Ala Gly Arg Gly Val Arg Glu Ala Asn
35 40 45

Gly Cys Phe Ala Glu Cys Phe Trp Gly Thr Asn Thr Ser Ser His Arg
50 55 60

Gly Cys Ser Leu Lys Lys Gly Gly Asp Arg Trp Gly Ala Phe Leu Thr
65 70 75 80

Tyr Ser Arg Asn Thr Cys Leu Phe Leu Lys Cys Phe His Leu Leu Lys
85 90 95

Lys Lys Lys Met Pro Pro Lys His Tyr Ala Gly His Glu Leu Leu Gln
100 105 110

Asn Val Glu Val Ile Lys Cys Asn Cys
115 120

<210> 136
<211> 232
<212> PRT
<213> Homo sapien

<400> 136

Met Ala Tyr His Ser Phe Leu Val Glu Pro Ile Ser Cys His Ala Trp
1 5 10 15

Asn Lys Asp Arg Thr Gln Ile Ala Ile Cys Pro Asn Asn His Glu Val
20 25 30

His Ile Tyr Glu Lys Ser Gly Ala Lys Trp Thr Lys Val His Glu Leu
35 40 45

Lys Glu His Asn Gly Gln Val Thr Gly Ile Asp Trp Ala Pro Glu Ser
50 55 60

125

Asn Arg Ile Val Thr Cys Gly Thr Asp Arg Asn Ala Tyr Val Trp Thr
65 70 75 80

Leu Lys Gly Arg Thr Trp Lys Pro Thr Leu Val Ile Leu Arg Ile Asn
85 90 95

Arg Ala Ala Arg Cys Val Arg Trp Ala Pro Asn Glu Asn Lys Phe Ala
100 105 110

Val Gly Ser Gly Ser Arg Val Ile Ser Ile Cys Tyr Phe Glu Gln Glu
115 120 125

Asn Asp Trp Trp Val Cys Lys His Ile Lys Lys Pro Ile Arg Ser Thr
130 135 140

Val Leu Ser Leu Asp Trp His Pro Asn Asn Val Leu Leu Ala Ala Gly
145 150 155 160

Ser Cys Asp Phe Lys Cys Arg Ile Phe Ser Ala Tyr Ile Lys Glu Val
165 170 175

Glu Glu Arg Pro Ala Pro Thr Pro Trp Gly Ser Lys Met Pro Phe Gly
180 185 190

Glu Leu Met Phe Glu Ser Ser Ser Cys Gly Trp Val His Gly Val
195 200 205

Cys Phe Ser Ala Ser Gly Ser Arg Val Ala Ser Ser Arg Leu Trp Pro
210 215 220

Leu Lys His Tyr His Cys Trp Arg
225 230

<210> 137
<211> 582
<212> PRT
<213> Homo sapien

<400> 137

Met Phe Tyr Tyr Pro Asn Val Leu Gln Arg His Thr Gly Cys Phe Ala
1 5 10 15

Thr Ile Trp Leu Ala Ala Thr Arg Gly Ser Arg Leu Val Lys Arg Glu
20 25 30

126

Tyr Leu Arg Val Asn Val Val Lys Thr Cys Glu Glu Ile Leu Asn Tyr
35 40 45

Val Leu Val Arg Val Gln Pro Pro Gln Pro Gly Leu Pro Arg Pro Arg
50 55 60

Phe Ser Leu Tyr Leu Ser Ala Gln Leu Gln Ile Gly Val Ile Arg Val
65 70 75 80

Tyr Ser Gln Gln Cys Gln Tyr Leu Val Glu Asp Ile Gln His Ile Leu
85 90 95

Glu Arg Leu His Arg Ala Gln Leu Gln Ile Arg Ile Asp Met Glu Thr
100 105 110

Glu Leu Pro Ser Leu Leu Pro Asn His Leu Ala Met Met Glu Thr
115 120 125

Leu Glu Asp Ala Pro Asp Pro Phe Phe Gly Met Met Ser Val Asp Pro
130 135 140

Arg Leu Pro Ser Pro Phe Asp Ile Pro Gln Ile Arg His Leu Leu Glu
145 150 155 160

Ala Ala Ile Pro Glu Arg Val Glu Glu Ile Pro Pro Glu Val Pro Thr
165 170 175

Glu Pro Arg Glu Pro Glu Arg Ile Pro Val Thr Val Leu Pro Pro Glu
180 185 190

Ala Ile Thr Ile Leu Glu Ala Glu Pro Ile Arg Met Leu Glu Ile Glu
195 200 205

Gly Glu Arg Glu Leu Pro Glu Val Ser Arg Arg Glu Leu Asp Leu Leu
210 215 220

Ile Ala Glu Glu Glu Ala Ile Leu Leu Glu Ile Pro Arg Leu Pro
225 230 235 240

Pro Pro Ala Pro Ala Glu Val Glu Gly Ile Gly Glu Ala Leu Gly Pro
245 250 255

Glu Glu Leu Arg Leu Thr Gly Trp Glu Pro Gly Ala Leu Leu Met Glu
260 265 270

Val Thr Pro Pro Glu Glu Leu Arg Leu Pro Ala Pro Pro Ser Pro Glu

127

275

280

285

Arg Arg Pro Pro Val Pro Pro Pro Arg Arg Arg Arg Arg Arg Arg
290 295 300

Leu Leu Phe Trp Asp Lys Glu Thr Gln Ile Ser Pro Glu Lys Phe Gln
305 310 315 320

Glu Gln Leu Gln Thr Arg Ala His Cys Trp Glu Cys Pro Met Val Gln
325 330 335

Pro Pro Glu Arg Thr Ile Arg Gly Pro Ala Glu Leu Phe Arg Thr Pro
340 345 350

Thr Leu Cys Lys Asn Gly Gly Trp Ala Arg Ser Ile Leu Lys Thr
355 360 365

Asn Ser Ser Phe Leu Val Leu Leu Thr Pro Gln Thr Leu Cys Leu Leu
370 375 380

Pro Ser Val Ser Thr Ala Gly Trp Leu Pro Pro Glu Leu Leu Gly Leu
385 390 395 400

Trp Thr His Cys Ala Gln Pro Pro Pro Lys Ala Leu Arg Arg Glu Leu
405 410 415

Pro Glu Glu Ala Ala Ala Glu Glu Glu Arg Arg Lys Ile Glu Val Pro
420 425 430

Ser Glu Ile Glu Val Pro Arg Glu Ala Leu Glu Pro Ser Val Pro Leu
435 440 445

Met Val Ser Leu Glu Ile Ser Leu Glu Ala Ala Glu Glu Glu Lys Ser
450 455 460

Arg Ile Ser Leu Ile Pro Pro Glu Glu Arg Trp Ala Trp Pro Glu Val
465 470 475 480

Glu Ala Pro Glu Ala Pro Ala Leu Pro Val Val Pro Glu Leu Pro Glu
485 490 495

Val Pro Met Glu Met Pro Leu Val Leu Pro Pro Glu Leu Glu Leu Leu
500 505 510

Ser Leu Glu Ala Val His Arg Ala Val Ala Leu Glu Leu Gln Ala Asn
515 520 525

128

Arg Glu Pro Asp Phe Ser Ser Leu Val Ser Pro Leu Ser Pro Arg Arg
530 535 540

Met Ala Ala Arg Val Phe Tyr Leu Leu Leu Val Leu Ser Ala Gln Gln
545 550 555 560

Ile Leu His Val Lys Gln Glu Lys Pro Tyr Gly Arg Leu Leu Ile Gln
565 570 575

Pro Gly Pro Arg Phe His
580

<210> 138
<211> 456
<212> PRT
<213> Homo sapien

<400> 138

Lys Thr Arg Gly Thr Met Phe Tyr Tyr Pro Asn Val Leu Gln Arg His
1 5 10 15

Thr Gly Cys Phe Ala Thr Ile Trp Leu Ala Ala Thr Arg Gly Ser Arg
20 25 30

Leu Val Lys Arg Glu Tyr Leu Arg Val Asn Val Val Lys Thr Cys Glu
35 40 45

Glu Ile Leu Asn Tyr Val Leu Val Arg Val Gln Pro Pro Gln Pro Gly
50 55 60

Leu Pro Arg Pro Arg Phe Ser Leu Tyr Leu Ser Ala Gln Leu Gln Ile
65 70 75 80

Gly Val Ile Arg Val Tyr Ser Gln Gln Cys Gln Tyr Leu Val Glu Asp
85 90 95

Ile Gln His Ile Leu Glu Arg Leu His Arg Ala Gln Leu Gln Ile Arg
100 105 110

Ile Asp Met Glu Thr Glu Leu Pro Ser Leu Leu Leu Pro Asn His Leu
115 120 125

Ala Met Met Glu Thr Leu Glu Asp Ala Pro Asp Pro Phe Phe Gly Met
130 135 140

129

Met Ser Val Asp Pro Arg Leu Pro Ser Pro Phe Asp Ile Pro Gln Ile
145 150 155 160

Arg His Leu Leu Glu Ala Ala Ile Pro Glu Arg Val Glu Glu Ile Pro
165 170 175

Pro Glu Val Pro Thr Glu Pro Arg Glu Pro Glu Arg Ile Pro Val Thr
180 185 190

Val Leu Pro Pro Glu Ala Ile Thr Ile Leu Glu Ala Glu Pro Ile Arg
195 200 205

Met Leu Glu Ile Glu Gly Glu Arg Glu Leu Pro Glu Val Ser Arg Arg
210 215 220

Glu Leu Asp Leu Leu Ile Ala Glu Glu Glu Ala Ile Leu Leu Glu
225 230 235 240

Ile Pro Arg Leu Pro Pro Pro Ala Pro Ala Glu Val Glu Gly Ile Gly
245 250 255

Glu Ala Leu Gly Pro Glu Glu Leu Arg Leu Thr Gly Trp Glu Pro Gly
260 265 270

Ala Leu Leu Met Glu Val Thr Pro Pro Glu Glu Leu Arg Leu Pro Ala
275 280 285

Pro Pro Ser Pro Glu Arg Arg Pro Pro Val Pro Pro Pro Pro Arg Arg
290 295 300

Arg Arg Arg Arg Arg Leu Leu Phe Trp Asp Lys Glu Thr Gln Ile Ser
305 310 315 320

Pro Glu Lys Phe Gln Glu Gln Leu Gln Thr Arg Ala His Cys Trp Glu
325 330 335

Cys Pro Met Val Gln Pro Pro Glu Arg Thr Ile Arg Gly Pro Ala Glu
340 345 350

Leu Phe Arg Thr Pro Thr Leu Cys Lys Asn Gly Gly Trp Ala Arg
355 360 365

Ser Ile Leu Lys Thr Asn Ser Ser Phe Leu Val Leu Leu Thr Pro Gln
370 375 380

Thr Leu Cys Leu Leu Pro Ser Cys Pro Gln Leu Ala Gly Tyr Pro Leu

130
385 390 395 400

Asn Tyr Trp Val Ser Gly Pro Ile Val Pro Ser His Pro Gln Lys Pro
405 410 415

Ser Gly Glu Ser Cys Leu Arg Arg Gln Pro Leu Arg Arg Lys Gly Glu
420 425 430

Arg Leu Lys Phe Gln Val Arg Leu Arg Ser Arg Gly Arg Pro Trp Ser
435 440 445

Pro Val Phe Pro Leu Trp Cys Leu
450 455

<210> 139
<211> 357
<212> PRT
<213> Homo sapien

<400> 139

Met Lys Ser Ser Arg Gly Val Gly Ile Cys Val Ala Ser Ser Asp Leu
1 5 10 15

Leu Ser Ser Asp Lys Ala Lys Arg Tyr Lys Lys Asn Leu Lys Ala Leu
20 25 30

Tyr Val Val His Pro Thr Ser Phe Ile Lys Val Leu Trp Asn Ile Leu
35 40 45

Lys Pro Leu Ile Ser His Lys Phe Gly Lys Lys Val Ile Tyr Phe Asn
50 55 60

Tyr Leu Ser Glu Leu His Glu His Leu Lys Tyr Asp Gln Leu Val Ile
65 70 75 80

Pro Pro Glu Val Leu Arg Tyr Asp Glu Lys Leu Gln Ser Leu His Glu
85 90 95

Gly Arg Thr Pro Pro Pro Thr Lys Thr Pro Pro Pro Arg Pro Pro Leu
100 105 110

Pro Thr Gln Gln Phe Gly Val Ser Leu Gln Tyr Leu Lys Asp Lys Asn
115 120 125

Gln Gly Glu Leu Ile Pro Pro Val Leu Arg Phe Thr Val Thr Tyr Leu
130 135 140

131

Arg Glu Lys Gly Leu Arg Thr Glu Gly Leu Phe Arg Arg Ser Ala Ser
145 150 155 160

Val Gln Thr Val Arg Glu Ile Gln Arg Leu Tyr Asn Gln Gly Lys Pro
165 170 175

Val Asn Phe Asp Asp Tyr Gly Asp Ile His Ile Pro Ala Val Ile Leu
180 185 190

Lys Thr Phe Leu Arg Glu Leu Pro Gln Pro Leu Leu Thr Phe Gln Ala
195 200 205

Tyr Glu Gln Ile Leu Gly Ile Thr Cys Val Glu Ser Ser Leu Arg Val
210 215 220

Thr Gly Cys Arg Gln Ile Leu Arg Ser Leu Pro Glu His Asn Tyr Val
225 230 235 240

Val Leu Arg Tyr Leu Met Gly Phe Leu His Ala Val Ser Arg Glu Ser
245 250 255

Ile Phe Asn Lys Met Asn Ser Ser Asn Leu Ala Cys Val Phe Gly Leu
260 265 270

Asn Leu Ile Trp Pro Ser Gln Gly Val Ser Ser Leu Ser Ala Leu Val
275 280 285

Pro Leu Asn Met Phe Thr Glu Leu Leu Ile Glu Tyr Tyr Glu Lys Ile
290 295 300

Phe Ser Thr Pro Glu Ala Pro Gly Glu His Gly Leu Ala Pro Trp Glu
305 310 315 320

Gln Gly Ser Arg Ala Ala Pro Leu Gln Glu Ala Val Pro Arg Thr Gln
325 330 335

Ala Thr Gly Leu Thr Lys Pro Thr Leu Pro Pro Ser Pro Leu Met Ala
340 345 350

Ala Arg Arg Arg Leu
355

<210> 140

<211> 337

<212> PRT

<213> Homo sapien

132

<400> 140

Gln Ser Gln Arg Tyr Lys Lys Asn Leu Lys Ala Leu Tyr Val Val His
1 5 10 15

Pro Thr Ser Phe Ile Lys Val Leu Trp Asn Ile Leu Lys Pro Leu Ile
20 25 30

Ser His Lys Phe Gly Lys Lys Val Ile Tyr Phe Asn Tyr Leu Ser Glu
35 40 45

Leu His Glu His Leu Lys Tyr Asp Gln Leu Val Ile Pro Pro Glu Val
50 55 60

Leu Arg Tyr Asp Glu Lys Leu Gln Ser Leu His Glu Gly Arg Thr Pro
65 70 75 80

Pro Pro Thr Lys Thr Pro Pro Pro Arg Pro Pro Leu Pro Thr Gln Gln
85 90 95

Phe Gly Val Ser Leu Gln Tyr Leu Lys Asp Lys Asn Gln Gly Glu Leu
100 105 110

Ile Pro Pro Val Leu Arg Phe Thr Val Thr Tyr Leu Arg Glu Lys Gly
115 120 125

Leu Arg Thr Glu Gly Leu Phe Arg Arg Ser Ala Ser Val Gln Thr Val
130 135 140

Arg Glu Ile Gln Arg Leu Tyr Asn Gln Gly Lys Pro Val Asn Phe Asp
145 150 155 160

Asp Tyr Gly Asp Ile His Ile Pro Ala Val Ile Leu Lys Thr Phe Leu
165 170 175

Arg Glu Leu Pro Gln Pro Leu Leu Thr Phe Gln Ala Tyr Glu Gln Ile
180 185 190

Leu Gly Ile Thr Cys Val Glu Ser Ser Leu Arg Val Thr Gly Cys Arg
195 200 205

Gln Ile Leu Arg Ser Leu Pro Glu His Asn Tyr Val Val Leu Arg Tyr
210 215 220

Leu Met Gly Phe Leu His Ala Val Ser Arg Glu Ser Ile Phe Asn Lys
225 230 235 240

133

Met Asn Ser Ser Asn Leu Ala Cys Val Phe Gly Leu Asn Leu Ile Trp
245 250 255

Pro Ser Gln Gly Val Ser Ser Leu Ser Ala Leu Val Pro Leu Asn Met
260 265 270

Phe Thr Glu Leu Leu Ile Glu Tyr Tyr Glu Lys Ile Phe Ser Thr Pro
275 280 285

Glu Ala Pro Gly Glu His Gly Leu Ala Pro Trp Glu Gln Gly Ser Arg
290 295 300

Ala Ala Pro Leu Gln Glu Ala Val Pro Arg Thr Gln Ala Thr Gly Leu
305 310 315 320

Thr Lys Pro Thr Leu Pro Pro Ser Pro Leu Met Ala Ala Arg Arg Arg
325 330 335

Leu

<210> 141
<211> 237
<212> PRT
<213> Homo sapien

<400> 141

Met Gly Arg Gly Val Ser Tyr Asn Val Leu Glu Ala Leu Trp Ala Gly
1 5 10 15

Thr Cys Glu Met Pro Gly Ser Ser Ser Pro Ala Gly Leu Arg Thr Glu
20 25 30

Gly Leu Phe Arg Arg Ser Ala Ser Val Gln Thr Val Arg Glu Ile Gln
35 40 45

Arg Leu Tyr Asn Gln Gly Lys Pro Val Asn Phe Asp Asp Tyr Gly Asp
50 55 60

Ile His Ile Pro Ala Val Ile Leu Lys Thr Phe Leu Arg Glu Leu Pro
65 70 75 80

Gln Pro Leu Leu Thr Phe Gln Ala Tyr Glu Gln Ile Leu Gly Ile Thr
85 90 95

134

Cys Val Glu Ser Ser Leu Arg Val Thr Gly Cys Arg Gln Ile Leu Arg
100 105 110

Ser Leu Pro Glu His Asn Tyr Val Val Leu Arg Tyr Leu Met Gly Phe
115 120 125

Leu His Ala Val Ser Arg Glu Ser Ile Phe Asn Lys Met Asn Ser Ser
130 135 140

Asn Leu Ala Cys Val Phe Gly Leu Asn Leu Ile Trp Pro Ser Gln Gly
145 150 155 160

Val Ser Ser Leu Ser Ala Leu Val Pro Leu Asn Met Phe Thr Glu Leu
165 170 175

Leu Ile Glu Tyr Tyr Glu Lys Ile Phe Ser Thr Pro Glu Ala Pro Gly
180 185 190

Glu His Gly Leu Ala Pro Trp Glu Gln Gly Ser Arg Ala Ala Pro Leu
195 200 205

Gln Glu Ala Val Pro Arg Thr Gln Ala Thr Gly Leu Thr Lys Pro Thr
210 215 220

Leu Pro Pro Ser Pro Leu Met Ala Ala Arg Arg Arg Leu
225 230 235

<210> 142
<211> 248
<212> PRT
<213> Homo sapien

<400> 142

Met Cys Gly Gly Gln Pro Gln Val Gly Asp Ala Met Gly Arg Gly Val
1 5 10 15

Ser Tyr Asn Val Leu Glu Ala Leu Trp Ala Gly Thr Cys Glu Met Pro
20 25 30

Gly Ser Ser Ser Pro Ala Gly Leu Arg Thr Glu Gly Leu Phe Arg Arg
35 40 45

Ser Ala Ser Val Gin Thr Val Arg Glu Ile Gln Arg Leu Tyr Asn Gln
50 55 60

Gly Lys Pro Val Asn Phe Asp Asp Tyr Gly Asp Ile His Ile Pro Ala
65 70 75 80

135

Val Ile Leu Lys Thr Phe Leu Arg Glu Leu Pro Gln Pro Leu Leu Thr
85 90 95

Phe Gln Ala Tyr Glu Gln Ile Leu Gly Ile Thr Cys Val Glu Ser Ser
100 105 110

Leu Arg Val Thr Gly Cys Arg Gln Ile Leu Arg Ser Leu Pro Glu His
115 120 125

Asn Tyr Val Val Leu Arg Tyr Leu Met Gly Phe Leu His Ala Val Ser
130 135 140

Arg Glu Ser Ile Phe Asn Lys Met Asn Ser Ser Asn Leu Ala Cys Val
145 150 155 160

Phe Gly Leu Asn Leu Ile Trp Pro Ser Gln Gly Val Ser Ser Leu Ser
165 170 175

Ala Leu Val Pro Leu Asn Met Phe Thr Glu Leu Leu Ile Glu Tyr Tyr
180 185 190

Glu Lys Ile Phe Ser Thr Pro Glu Ala Pro Gly Glu His Gly Leu Ala
195 200 205

Pro Trp Glu Gln Gly Ser Arg Ala Ala Pro Leu Gln Glu Ala Val Pro
210 215 220

Arg Thr Gln Ala Thr Gly Leu Thr Lys Pro Thr Leu Pro Pro Ser Pro
225 230 235 240

Leu Met Ala Ala Arg Arg Arg Leu
245

<210> 143
<211> 113
<212> PRT
<213> Homo sapien

<400> 143

Met Gly Phe Phe Ser Arg Arg Thr Phe Cys Gly Arg Ser Gly Arg Ser
1 5 10 15

Cys Arg Gly Gln Leu Val Gln Val Ser Arg Pro Glu Val Ser Ala Gly
20 25 30

136

Ser Leu Leu Leu Pro Ala Pro Gln Ala Glu Asp His Ser Ser Arg Ile
35 40 45

Leu Tyr Pro Arg Pro Lys Ser Leu Leu Pro Lys Met Met Asn Ala Asp
50 55 60

Met Asp Asp Leu Ser Ala Arg Val Asp Ala Val Lys Glu Glu Asn Leu
65 70 75 80

Lys Leu Lys Ser Glu Asn Gln Val Leu Gly Gln Tyr Ile Glu Asn Leu
85 90 95

Met Ser Ala Ser Ser Val Phe Gln Thr Thr Asp Thr Lys Ser Lys Arg
100 105 110

Lys

<210> 144

<211> 81

<212> PRT

<213> Homo sapien

<400> 144

Met Ala Pro Trp Ser Gly Lys Ala Arg Pro Thr Leu Phe Ser Pro Arg
1 5 10 15

Ala Leu Cys Thr Arg Val Cys Cys Arg Cys Val Arg Gln Gly Gly Glu
20 25 30

Asn Pro Gly Ala Arg Ala Ala Ser His Leu Leu Leu Gln Gly Leu Cys
35 40 45

Gly Cys Val Ile Ser Trp Val Lys Ile Met Val Pro Gly Arg Glu Leu
50 55 60

Asp Pro Ala Phe Pro Glu Asn Phe Trp Lys Asn Leu Lys Lys Glu Asn
65 70 75 80

Ile

<210> 145.

<211> 126

<212> PRT

<213> Homo sapien

<400> 145

Phe Gly Thr Arg Gly Arg Arg Gly Ser Ser Phe Thr Ser Ala Gly Arg
1 5 10 15

Leu Glu Lys Pro Arg Asn Ser Ser Phe Phe Leu Pro Pro Pro Ser Leu
20 25 30

Arg Val Ser Val Leu Arg Arg Ala Leu Gly Ala Asn Arg Gly Ala Arg
35 40 45

Arg Gly Asp Arg Pro Pro Ser Leu Gly Gly Ala Arg Gly Leu Ala Ala
50 55 60

Thr Ala Gly Ala Ser Ala Pro Ala Arg Trp Val Ile Phe Ser Arg Val
65 70 75 80

Ala Arg Ala Gly Leu Arg Val Ser Leu Arg Arg Tyr Thr Arg Ala Glu
85 90 95

Tyr Glu Ser Glu Ala Glu Gly Val Met Gly Glu Ser Arg Val Ala Pro
100 105 110

Arg Pro Ala Gly Pro Gly Leu Ser Glu Ala Tyr Gly Asp Pro
115 120 125

<210> 146

<211> 126

<212> PRT

<213> Homo sapien

<400> 146

Met Tyr Ser Thr Val Ala Leu Pro Val Asp Asn Val Ile Thr Phe Ser
1 5 10 15

Phe Cys Phe Lys Thr Phe Leu Phe Leu Gln Ala Gly Gln Ala Phe Arg
20 25 30

Lys Phe Leu Pro Leu Phe Asp Arg Val Leu Val Glu Arg Ser Ala Ala
35 40 45

Glu Thr Val Thr Lys Gly Gly Ile Met Leu Pro Glu Lys Ser Gln Gly
50 55 60

Lys Val Leu Gln Ala Thr Val Val Ala Val Gly Ser Gly Ser Lys Gly
65 70 75 80

Lys Gly Gly Glu Ile Gln Pro Val Ser Val Lys Val Gly Asp Lys Val

138
85 90 95

Leu Leu Pro Glu Tyr Gly Gly Thr Lys Val Val Leu Asp Asp Lys Val
100 105 110

Cys Lys Leu Asn Asn Ser Lys Lys Lys Ser Asp Ile Cys Asn
115 120 125

<210> 147
<211> 162
<212> PRT
<213> Homo sapien

<400> 147

Met Leu Tyr Met Ala Cys Val Ser Leu Leu Phe Ser Arg Arg His His
1 5 10 15

His Ser Cys Pro Leu Leu Glu Gly Ser Ile Ser Cys Trp Ser Gly Leu
20 25 30

His Lys Leu Ser Val Leu Ser Leu Val Leu Ala Ile Pro Leu Pro Gly
35 40 45

Gln Cys Asp Leu Arg Arg Val Glu Ala Gln Gly Pro Ala Pro Gln Gly
50 55 60

Gly Leu Met Val Arg Asp Gly Val Val Gly His Val Cys Leu Trp Gly
65 70 75 80

Val Arg Ala Leu Gln Arg Leu Leu Pro Val Leu Gln Val Ser Ala Glu
85 90 95

Pro Leu His Ala Arg Ala Leu Gln Val Gly Ser Asp Leu Leu Arg His
100 105 110

Thr Gly Arg Leu Pro Leu Ala Leu Gly Asp Leu Ser Arg Gly Val Arg
115 120 125

Arg Gly Pro Gly Ala Gln Val Leu Val Gln Gly Asp Val Ile Leu Ala
130 135 140

Val Val Gly Val Leu Val Met Pro Ala Glu Glu Ala Pro Val Arg Pro
145 150 155 160

His Val

139

<210> 148
<211> 201
<212> PRT
<213> Homo sapien

<400> 148

Arg Asp Pro Leu Arg Leu His Pro Leu Asp Ser Gln Ala Ser Asn Asn
1 5 10 15

Ala His Asp Gly Asp Gly Gly Leu Gly Arg Trp Leu Pro Ser Gln Gly
20 25 30

Glu Gly Leu Arg Gln Pro Leu Met Leu Tyr Met Ala Cys Val Ser Leu
35 40 45

Leu Phe Ser Arg Arg His His Ser Cys Pro Leu Leu Glu Gly Ser
50 55 60

Ile Ser Cys Trp Ser Gly Leu His Lys Leu Ser Val Leu Ser Leu Val
65 70 75 80

Leu Ala Ile Pro Leu Pro Gly Gln Cys Asp Leu Arg Arg Val Glu Ala
85 90 95

Gln Gly Pro Ala Pro Gln Gly Gly Leu Met Val Arg Asp Gly Val Val
100 105 110

Gly His Val Cys Leu Trp Gly Val Arg Ala Leu Gln Arg Leu Leu Pro
115 120 125

Val Leu Gln Val Ser Ala Glu Pro Leu His Ala Arg Ala Leu Gln Val
130 135 140

Gly Ser His Leu Leu Arg His Thr Gly Arg Leu Pro Leu Ala Leu Gly
145 150 155 160

Asp Leu Ser Arg Gly Val Arg Arg Gly Pro Gly Ala Gln Val Leu Val
165 170 175

Gln Gly Asp Val Ile Leu Ala Val Val Gly Val Leu Val Met Pro Ala
180 185 190

Glu Glu Ala Pro Val Arg Pro His Val
195 200

<210> 149

140

<211> 168
<212> PRT
<213> Homo sapien

<400> 149

Met Arg Ser Gln Tyr Glu Val Met Ala Glu Gln Asn Arg Lys Asp Ala
1 5 10 15

Glu Ala Trp Phe Thr Ser Arg Thr Glu Glu Leu Asn Arg Glu Val Ala
20 25 30

Gly His Thr Glu Gln Leu Gln Met Ser Arg Ser Glu Val Thr Asp Leu
35 40 45

Arg Arg Thr Leu Gln Gly Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser
50 55 60

Met Lys Ala Ala Leu Glu Asp Thr Leu Ala Glu Thr Glu Ala Arg Phe
65 70 75 80

Gly Ala Gln Leu Ala His Ile Gln Ala Leu Ile Ser Gly Ile Glu Ala
85 90 95

Gln Leu Gly Asp Val Arg Ala Asp Ser Glu Arg Gln Asn Gln Glu Tyr
100 105 110

His Thr Ser Gly Ser Trp Thr Ser Ser Arg Gly Trp Ser Arg Arg Leu
115 120 125

Pro Pro Thr Ala Ala Cys Ser Arg Asp Arg Lys Ile Thr Thr Thr Ile
130 135 140

Cys Leu Pro Pro Arg Ser Ser Glu Ala Ala Gly Ser Gly Ala Ser Ala
145 150 155 160

Val Leu Trp Arg Val Ser Ser Gly
165

<210> 150
<211> 194
<212> PRT
<213> Homo sapien

<400> 150

His Ala Arg Ala Ala Leu Cys Asp Gly Cys Val Val Ala Ala Glu Ile
1 5 10 15

141

Ser Thr Leu Arg Gly Gln Val Gly Gly Gln Val Ser Val Glu Val Asp
 20 25 30

Ser Ala Pro Gly Thr Asp Leu Ala Lys Ile Leu Ser Asp Met Arg Ser
 35 40 45

Gln Tyr Glu Val Met Ala Glu Gln Asn Arg Lys Asp Ala Glu Ala Trp
 50 55 60

Phe Thr Ser Arg Thr Glu Glu Leu Asn Arg Glu Val Ala Gly His Thr
 65 70 75 80

Glu Gln Leu Gln Met Ser Arg Ser Glu Val Thr Asp Leu Arg Arg Thr
 85 90 95

Leu Gln Gly Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala
 100 105 110

Ala Leu Glu Asp Thr Leu Ala Glu Thr Glu Ala Arg Phe Gly Ala Gln
 115 120 125

Leu Ala His Ile Gln Ala Leu Ile Ser Gly Ile Glu Ala Gln Leu Gly
 130 135 140

Asp Val Arg Ala Asp Ser Glu Arg Gln Asn Gln Glu Tyr Gln Arg Leu
 145 150 155 160

Met Asp Ile Lys Ser Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Ser
 165 170 175

Leu Leu Glu Gly Gln Glu Asp His Tyr Asn Asn Leu Ser Ala Ser Lys
 180 185 190

Val Leu

<210> 151
 <211> 265
 <212> PRT
 <213> Homo sapien

<400> 151

Met Thr Ser Tyr Ser Tyr Arg Gln Ser Ser Ala Thr Ser Ser Phe Gly
 1 5 10 15

Gly Leu Gly Gly Ser Val Arg Phe Gly Pro Gly Val Ala Phe Arg
 20 25 30

142

Ala Pro Ser Ile His Gly Gly Ser Gly Gly Arg Gly Val Ser Val Ser
35 40 45

Ser Ala Arg Phe Val Ser Ser Ser Ser Gly Gly Tyr Gly Gly Gly
50 55 60

Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly Leu Leu Ala Gly Asn Glu
65 70 75 80

Lys Leu Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95

Lys Val Arg Ala Leu Glu Ala Ala Asn Gly Glu Leu Glu Val Lys Ile
100 105 110

Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly Pro Ser Arg Asp Tyr Ser
115 120 125

His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg Asp Lys Ile Leu Gly Ala
130 135 140

Thr Ile Glu Asn Ser Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu
145 150 155 160

Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg
165 170 175

Met Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu
180 185 190

Leu Thr Leu Ala Arg Thr Asp Leu Glu Met Gln Ile Glu Gly Leu Lys
195 200 205

Glu Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Ile Ser Thr
210 215 220

Leu Arg Trp Gly Pro Gln Arg Val Gly Gly Asn Gly Gly Pro Arg Val
225 230 235 240

Pro Arg Cys Trp Thr Val Asp Pro Leu Gly His Asp Leu Ala Asp Leu
245 250 255

Ser Asp Met Arg Ala Tyr Glu Ser Cys
260 265

<210> 152
<211> 69
<212> PRT
<213> Homo sapien

<400> 152

Cys Arg Ala Ala Gln Cys Asp Gly Ser Ala Ala Arg Ala Gly Thr Ser
1 5 10 15

Gly Ser Trp Thr Ser Ser Arg Gly Trp Ser Arg Arg Leu Pro Pro Thr
20 25 30

Ala Ala Cys Ser Arg Asp Arg Lys Ile Thr Thr Thr Ile Cys Leu Pro
35 40 45

Pro Arg Ser Ser Glu Ala Ala Gly Ser Gly Ala Ser Ala Val Leu Trp
50 55 60

Arg Val Ser Ser Gly
65

<210> 153
<211> 79
<212> PRT
<213> Homo sapien

<400> 153

Trp Ile Gly Arg Pro Gly Arg Ala Ala His Gly His Gln Val Ala Ala
1 5 10 15

Gly Ala Gly Asp Cys His Leu Pro Gln Pro Ala Arg Gly Thr Gly Arg
20 25 30

Ser Leu Gln Gln Phe Val Cys Leu Gln Gly Pro Leu Arg Gln Gln Ala
35 40 45

Leu Gly Leu Leu Leu Ser Phe Gly Gly Cys Leu Leu Gly Arg Gly Met
50 55 60

Gly Arg Lys Gly Pro Leu Pro Pro Ala Leu Leu Leu Thr Cys Gln
65 70 75

<210> 154
<211> 56
<212> PRT
<213> Homo sapien

<400> 154

144

Arg Pro Pro Thr Thr Thr Ala Arg Ile Gln Ala Ser Asn Asp Val
1 5 10 15

Arg Gly Tyr Gln Arg Leu Met Asp Ile Lys Ser Arg Leu Glu Gln Glu
20 25 30

Ile Ala Thr Tyr Arg Ser Leu Leu Glu Gly Gln Glu Asp His Tyr Asn
35 40 45

Asn Leu Ser Ala Ser Lys Val Leu
50 55

<210> 155

<211> 90

<212> PRT

<213> Homo sapien

<400> 155

Arg Pro Pro Thr Thr Thr Ala Arg Ile Gln Ala Ser Asn Asp Val
1 5 10 15

Arg Gly Ala Ala His Gly His Gln Val Ala Ala Gly Ala Gly Asp Cys
20 25 30

His Leu Pro Gln Pro Ala Arg Gly Thr Gly Arg Ser Leu Gln Gln Phe
35 40 45

Val Cys Leu Gln Gly Pro Leu Arg Gln Gln Ala Leu Gly Leu Leu Leu
50 55 60

Ser Phe Gly Gly Cys Leu Leu Gly Arg Gly Met Gly Arg Lys Gly Pro
65 70 75 80

Leu Pro Pro Ala Leu Leu Leu Thr Cys Gln
85 90

<210> 156

<211> 315

<212> PRT

<213> Homo sapien

<400> 156

Met Thr Ser Tyr Ser Tyr Arg Gln Ser Ser Ala Thr Ser Ser Phe Gly
1 5 10 15

Gly Leu Gly Gly Ser Val Arg Phe Gly Pro Gly Val Ala Phe Arg
20 25 30

145

Ala Pro Ser Ile His Gly Gly Ser Gly Gly Arg Gly Val Ser Val Ser
35 40 45

Ser Ala Arg Phe Val Ser Ser Ser Ser Gly Gly Tyr Gly Gly Gly
50 55 60

Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly Leu Leu Ala Gly Asn Glu
65 70 75 80

Lys Leu Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp
85 90 95

Lys Val Arg Ala Leu Glu Ala Ala Asn Gly Glu Leu Glu Val Lys Ile
100 105 110

Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly Pro Ser Arg Asp Tyr Ser
115 120 125

His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg Asp Lys Ile Leu Gly Ala
130 135 140

Thr Ile Glu Asn Ser Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu
145 150 155 160

Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg
165 170 175

Met Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu
180 185 190

Leu Thr Leu Ala Arg Thr Asp Leu Glu Met Gln Ile Glu Gly Leu Lys
195 200 205

Glu Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Ile Ser Thr
210 215 220

Leu Arg Gly Gln Val Gly Gly Gln Val Ser Val Glu Val Asp Ser Ala
225 230 235 240

Pro Gly Thr Asp Leu Ala Lys Ile Leu Ser Asp Met Arg Ser Gln Tyr
245 250 255

Glu Val Met Ala Glu Gln Asn Arg Lys Asp Ala Glu Ala Trp Phe Thr
260 265 270

146

Ser Arg Leu Lys Ile Val Pro Gly Ala Leu Ala His Glu Glu Pro Lys
275 280 285

Asn Gly Arg Tyr Ala Gln Gly Pro Gln Val Lys Arg Gly Thr Glu Ser
290 295 300

Cys Asn Thr Lys Gly Gly Cys Gln His Thr Pro
305 310 315

<210> 157
<211> 338
<212> PRT
<213> Homo sapien

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> X=any amino acid

<220>
<221> MISC_FEATURE
<222> (304)..(305)
<223> X=any amino acid

<220>
<221> MISC_FEATURE
<222> (308)..(309)
<223> X=any amino acid

<220>
<221> MISC_FEATURE
<222> (312)..(313)
<223> X=any amino acid

<220>
<221> MISC_FEATURE
<222> (315)..(317)
<223> X=any amino acid

<400> 157

Val Glu Ala Gly Val Asn Arg Xaa Arg Ala Ala Ser Glu Thr Arg Val
1 5 10 15

Ala Pro Ser Val Leu Arg Leu Ala Met Thr Ser Tyr Ser Tyr Arg Gln
20 25 30

Ser Ser Ala Thr Ser Ser Phe Gly Gly Leu Gly Gly Ser Val Arg
35 40 45

147

Phe Gly Pro Gly Val Ala Phe Arg Ala Pro Ser Ile His Gly Gly Ser
50 55 60

Gly Gly Arg Gly Val Ser Val Ser Ser Ala Arg Phe Val Ser Ser Ser
65 70 75 80

Ser Ser Gly Gly Tyr Gly Gly Tyr Gly Gly Val Leu Thr Ala Ser
85 90 95

Asp Gly Leu Leu Ala Gly Asn Glu Lys Leu Thr Met Gln Asn Leu Asn
100 105 110

Asp Arg Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Ala Ala
115 120 125

Asn Gly Glu Leu Glu Val Lys Ile Arg Asp Trp Tyr Gln Lys Gln Gly
130 135 140

Pro Gly Pro Ser Arg Asp Tyr Ser His Tyr Tyr Thr Thr Ile Gln Asp
145 150 155 160

Leu Arg Asp Lys Ile Leu Gly Ala Thr Ile Glu Asn Ser Arg Ile Val
165 170 175

Leu Gln Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg Thr Lys
180 185 190

Phe Glu Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn
195 200 205

Gly Leu Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu
210 215 220

Glu Met Gln Ile Glu Gly Leu Lys Glu Glu Leu Ala Tyr Leu Lys Lys
225 230 235 240

Asn His Glu Glu Glu Ile Ser Thr Leu Arg Gly Gln Val Gly Gly Gln
245 250 255

Val Ser Val Glu Val Asp Ser Ala Pro Gly Thr Asp Leu Ala Lys Ile
260 265 270

Leu Ser Asp Met Arg Ser Gln Tyr Glu Val Met Ala Glu Gln Asn Arg
275 280 285

148

Lys Asp Ala Glu Ala Trp Phe Thr Ser Arg Leu Lys Ile Asp Gly Xaa
290 295 300

Xaa Ala His Xaa Xaa Pro Lys Xaa Xaa Arg Xaa Xaa Xaa Ala Pro Arg
305 310 315 320

Leu Arg Gly Ala His Arg Ala Val Thr Pro Lys Gly Val Ala Ser Ile
325 330 335

Arg Arg

<210> 158

<211> 266

<212> PRT

<213> Homo sapien

<400> 158

Met Leu Arg Lys Leu Cys Leu Ala Ala Thr Ile Ser Phe Glu Arg Phe
1 5 10 15

Glu Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn Gly
20 25 30

Leu Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu Glu
35 40 45

Met Gln Ile Glu Gly Leu Lys Glu Glu Leu Ala Tyr Leu Lys Lys Asn
50 55 60

His Glu Glu Glu Ile Ser Thr Leu Arg Gly Gln Val Gly Gly Gln Val
65 70 75 80

Ser Val Glu Val Asp Ser Ala Pro Gly Thr Asp Leu Ala Lys Ile Leu
85 90 95

Ser Asp Met Arg Ser Gln Tyr Glu Val Met Ala Glu Gln Asn Arg Lys
100 105 110

Asp Ala Glu Ala Trp Phe Thr Ser Arg Thr Glu Glu Leu Asn Arg Glu
115 120 125

Val Ala Gly His Thr Glu Gln Leu Gln Met Ser Arg Ser Glu Val Thr
130 135 140

Asp Leu Arg Arg Thr Leu Gln Gly Leu Glu Ile Glu Leu Gln Ser Gln
145 150 155 160

149

Leu Ser Met Lys Ala Ala Leu Glu Asp Thr Leu Ala Glu Thr Glu Ala
165 170 175

Arg Phe Gly Ala Gln Leu Ala His Ile Gln Ala Leu Ile Ser Gly Ile
180 185 190

Glu Ala Gln Leu Gly Asp Val Arg Ala Asp Ser Glu Arg Gln Asn Gln
195 200 205

Glu Tyr His Thr Ser Gly Ser Trp Thr Ser Ser Arg Gly Trp Ser Arg
210 215 220

Arg Leu Pro Pro Thr Ala Ala Cys Ser Arg Asp Arg Lys Ile Thr Thr
225 230 235 240

Thr Ile Cys Leu Pro Pro Arg Ser Ser Glu Ala Ala Gly Ser Gly Ala
245 250 255

Ser Ala Val Leu Trp Arg Val Ser Ser Gly
260 265

<210> 159

<211> 263

<212> PRT

<213> Homo sapien

<400> 159

Pro Pro Tyr Gly Leu Leu Asn Ser Gly Glu Val Gly Lys Ser Ser Glu
1 5 10 15

Met Leu Arg Lys Leu Cys Leu Ala Ala Thr Ile Ser Phe Glu Arg Phe
20 25 30

Glu Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn Gly
35 40 45

Leu Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu Glu
50 55 60

Met Gln Ile Glu Gly Leu Lys Glu Glu Leu Ala Tyr Leu Lys Lys Asn
65 70 75 80

His Glu Glu Glu Ile Ser Thr Leu Arg Gly Gln Val Gly Gly Gln Val
85 90 95

150

Ser Val Glu Val Asp Ser Ala Pro Gly Thr Asp Leu Ala Lys Ile Leu
100 105 110

Ser Asp Met Arg Ser Gln Tyr Glu Val Met Ala Glu Gln Asn Arg Lys
115 120 125

Asp Ala Glu Ala Trp Phe Thr Ser Arg Thr Glu Glu Leu Asn Arg Glu
130 135 140

Val Ala Gly His Thr Glu Gln Leu Gln Met Ser Arg Ser Glu Val Thr
145 150 155 160

Asp Leu Arg Arg Thr Leu Gln Gly Leu Glu Ile Glu Leu Gln Ser Gln
165 170 175

Leu Ser Met Lys Ala Ala Leu Glu Asp Thr Leu Ala Glu Thr Glu Ala
180 185 190

Arg Phe Gly Ala Gln Leu Ala His Ile Gln Ala Leu Ile Ser Gly Ile
195 200 205

Glu Ala Gln Leu Gly Asp Val Arg Ala Asp Ser Glu Arg Gln Asn Gln
210 215 220

Glu Tyr Gln Arg Leu Met Asp Ile Lys Ser Arg Leu Glu Gln Glu Ile
225 230 235 240

Ala Thr Tyr Arg Ser Leu Leu Glu Gly Gln Glu Asp His Tyr Asn Asn
245 250 255

Leu Ser Ala Ser Lys Val Leu
260

<210> 160
<211> 107
<212> PRT
<213> Homo sapien

<400> 160

Met Ser Arg Ser Val Ala Leu Ala Val Leu Ala Leu Leu Ser Leu Ser
1 5 10 15

Gly Leu Glu Ala Ile Gln Arg Thr Pro Lys Ile Gln Val Tyr Ser Arg
20 25 30

His Pro Ala Glu Asn Gly Lys Ser Asn Phe Leu Asn Cys Tyr Val Ser
35 40 45

Gly Phe His Pro Ser Asp Ile Glu Val Asp Leu Leu Lys Asn Gly Glu
50 55 60

Arg Ile Glu Lys Val Glu His Ser Asp Leu Ser Phe Ser Lys Asp Trp
65 70 75 80

Ser Phe Tyr Leu Leu Tyr Tyr Thr Glu Phe Thr Pro Thr Glu Lys Asp
85 90 95

Glu Ser Arg His Val Ser Ser Ile Met Glu Val
100 105

<210> 161

<211> 41

<212> PRT

<213> Homo sapien

<400> 161

Met Asp Gly Arg Pro Gly Arg Tyr Tyr Thr Glu Phe Thr Pro Thr Glu
1 5 10 15

Lys Asp Glu Tyr Ala Cys Arg Val Asn His Val Thr Leu Ser Gln Pro
20 25 30

Lys Ile Val Lys Trp Asp Arg Asp Met
35 40

<210> 162

<211> 47

<212> PRT

<213> Homo sapien

<400> 162

Ala Ala Ser Trp Arg Phe Glu Asp Ala Ala Phe Gly Leu Asp Glu Phe
1 5 10 15

Gln Ile Leu Leu Ala Cys Phe Leu Ile Leu Ile Cys Leu Tyr Thr Tyr
20 25 30

Thr Leu Cys Thr Lys Cys Arg Val Ile Ile Met Leu Thr Trp Thr
35 40 45

<210> 163

<211> 257

<212> PRT

<213> Homo sapien

152

<400> 163

Met Ser Gly Glu Glu Asn Pro Ala Ser Lys Pro Thr Pro Val Gln Asp
1 5 10 15

Val Gln Gly Asp Gly Arg Trp Met Ser Leu His His Arg Phe Val Ala
20 25 30

Asp Ser Lys Asp Lys Glu Pro Glu Val Val Phe Ile Gly Asp Ser Leu
35 40 45

Val Gln Leu Met His Gln Cys Glu Ile Trp Arg Glu Leu Phe Ser Pro
50 55 60

Leu His Ala Leu Asn Phe Gly Ile Gly Gly Asp Gly Thr Gln His Val
65 70 75 80

Leu Trp Arg Leu Glu Asn Gly Glu Leu Glu His Ile Arg Pro Lys Val
85 90 95

Ser Gly Ala Trp Val Gly Leu Tyr Asn Ile Phe Trp Leu Pro Pro His
100 105 110

Arg Cys Phe Met Ser Leu Phe Pro Gln Ile Val Val Trp Val Gly
115 120 125

Thr Asn Asn His Gly His Thr Ala Glu Gln Val Thr Gly Gly Ile Lys
130 135 140

Ala Ile Val Gln Leu Val Asn Glu Arg Gln Pro Gln Ala Arg Val Val
145 150 155 160

Val Leu Gly Leu Leu Pro Arg Gly Gln His Pro Asn Pro Leu Arg Glu
165 170 175

Lys Asn Arg Gln Val Asn Glu Leu Val Arg Ala Ala Leu Ala Gly His
180 185 190

Pro Arg Ala His Phe Leu Asp Ala Asp Pro Gly Phe Val His Ser Asp
195 200 205

Gly Thr Ile Ser His His Asp Met Tyr Asp Tyr Leu His Leu Ser Arg
210 215 220

Leu Gly Tyr Thr Pro Val Cys Arg Ala Leu His Ser Leu Leu Leu Arg
225 230 235 240

153

Leu Leu Ala Gln Asp Gln Gly Gln Gly Ala Pro Leu Leu Glu Pro Ala
245 250 255

Pro

<210> 164

<211> 292

<212> PRT

<213> Homo sapien

<400> 164

Met Ala Ala Thr Ser Leu Met Ser Ala Leu Ala Ala Arg Leu Leu Gln
1 5 10 15

Pro Ala His Ser Cys Ser Leu Arg Leu Arg Pro Phe His Leu Ala Ala
20 25 30

Val Arg Asn Glu Ala Val Val Ile Ser Gly Arg Lys Leu Ala Gln Gln
35 40 45

Ile Lys Gln Glu Val Arg Gln Glu Val Glu Glu Trp Val Ala Ser Gly
50 55 60

Asn Lys Arg Pro His Leu Ser Val Ile Leu Val Gly Glu Asn Pro Ala
65 70 75 80

Ser His Ser Tyr Val Leu Asn Lys Thr Arg Ala Ala Ala Val Val Gly
85 90 95

Ile Asn Ser Glu Thr Ile Met Lys Pro Ala Ser Ile Ser Glu Glu Glu
100 105 110

Leu Leu Asn Leu Ile Asn Lys Leu Asn Asn Asp Asp Asn Val Asp Gly
115 120 125

Leu Leu Val Gln Leu Pro Leu Pro Glu His Ile Asp Glu Arg Arg Ile
130 135 140

Cys Asn Ala Val Ser Pro Asp Lys Asp Val Asp Gly Phe His Val Ile
145 150 155 160

Asn Val Gly Arg Met Cys Leu Asp Gln Tyr Ser Met Leu Pro Ala Thr
165 170 175

Pro Trp Gly Val Trp Glu Ile Ile Lys Arg Thr Gly Ile Pro Thr Leu

154

180

185

190

Gly Lys Asn Val Val Val Ala Gly Arg Ser Lys Asn Val Gly Met Pro
195 200 205

Ile Ala Met Leu Leu His Thr Asp Gly Ala His Glu Arg Pro Gly Gly
210 215 220

Asp Ala Thr Val Thr Ile Ser His Arg Tyr Thr Pro Lys Glu Gln Leu
225 230 235 240

Lys Lys His Thr Ile Leu Ala Asp Ile Val Ile Ser Ala Ala Gly Met
245 250 255

Ser Leu Gln Leu Leu Phe Gln Ser Ile Ile Asp Glu Arg Arg Ile Cys
260 265 270

Asn Ala Val Ser Pro Asp Lys Asp Val Asp Gly Phe His Val Ile Thr
275 280 285

Val Gly Arg Met
290

<210> 165
<211> 307
<212> PRT
<213> Homo sapien

<400> 165

Tyr Asn Arg Val Ala Arg Ala Arg Ala Ser Leu Pro Ala Gln Ser Pro
1 5 10 15

Ala Arg Ser Met Ala Ala Thr Ser Leu Met Ser Ala Leu Ala Ala Arg
20 25 30

Leu Leu Gln Pro Ala His Ser Cys Ser Leu Arg Leu Arg Pro Phe His
35 40 45

Leu Ala Ala Val Arg Asn Glu Ala Val Val Ile Ser Gly Arg Lys Leu
50 55 60

Ala Gln Gln Ile Lys Gln Glu Val Arg Gln Glu Val Glu Glu Trp Val
65 70 75 80

Ala Ser Gly Asn Lys Arg Pro His Leu Ser Val Ile Leu Val Gly Glu
85 90 95

155

Asn Pro Ala Ser His Ser Tyr Val Leu Asn Lys Thr Arg Ala Ala Ala
100 105 110

Val Val Gly Ile Asn Ser Glu Thr Ile Met Lys Pro Ala Ser Ile Ser
115 120 125

Glu Glu Glu Leu Leu Asn Leu Ile Asn Lys Leu Asn Asn Asp Asp Asn
130 135 140

Val Asp Gly Leu Leu Val Gln Leu Pro Leu Pro Glu His Ile Asp Glu
145 150 155 160

Arg Arg Ile Cys Asn Ala Val Ser Pro Asp Lys Asp Val Asp Gly Phe
165 170 175

His Val Ile Asn Val Gly Arg Met Cys Leu Asp Gln Tyr Ser Met Leu
180 185 190

Pro Ala Thr Pro Trp Gly Val Trp Glu Ile Ile Lys Arg Thr Gly Ile
195 200 205

Pro Thr Leu Gly Lys Asn Val Val Val Ala Gly Arg Ser Lys Asn Val
210 215 220

Gly Met Pro Ile Ala Met Leu Leu His Thr Asp Gly Ala His Glu Arg
225 230 235 240

Pro Gly Gly Asp Ala Thr Val Thr Ile Ser His Arg Tyr Thr Pro Lys
245 250 255

Glu Gln Leu Lys Lys His Thr Ile Leu Ala Asp Ile Val Ile Ser Ala
260 265 270

Ala Gly Met Ser Leu Gln Leu Leu Phe Gln Ser Ile Leu Met Arg Glu
275 280 285

Gly Ser Ala Met Leu Phe Leu Gln Thr Arg Met Leu Met Ala Phe Met
290 295 300

Leu Leu Leu
305

<210> 166
<211> 207
<212> PRT
<213> Homo sapien

156

<400> 166

Met Asp Arg Gly Glu Gln Gly Leu Leu Arg Thr Asp Pro Val Pro Glu
1 5 10 15

Glu Gly Glu Asp Val Ala Ala Thr Ile Ser Ala Thr Glu Thr Leu Ser
20 25 30

Glu Glu Glu Gln Glu Glu Leu Arg Arg Glu Leu Ala Lys Val Glu Glu
35 40 45

Glu Ile Gln Thr Leu Ser Gln Val Leu Ala Ala Lys Glu Lys His Leu
50 55 60

Ala Glu Ile Lys Arg Lys Leu Gly Ile Asn Ser Leu Gln Glu Leu Lys
65 70 75 80

Gln Asn Ile Ala Lys Gly Trp Gln Asp Val Thr Ala Thr Ser Ala Tyr
85 90 95

Lys Lys Thr Ser Glu Thr Leu Ser Gln Ala Gly Gln Lys Ala Ser Ala
100 105 110

Ala Phe Ser Ser Val Gly Ser Val Ile Thr Lys Lys Leu Glu Asp Val
115 120 125

Lys Leu Gln Ala Phe Ser His Ser Phe Ser Ile Arg Ser Ile Gln His
130 135 140

Ser Ile Ser Met Pro Ala Met Arg Asn Ser Pro Thr Phe Lys Ser Phe
145 150 155 160

Glu Glu Lys Val Glu Asn Leu Lys Ser Lys Val Gly Gly Thr Lys Pro
165 170 175

Ala Gly Gly Asp Phe Gly Glu Val Leu Asn Ser Ala Ala Asn Ala Ser
180 185 190

Ala Thr Thr Thr Glu Pro Leu Pro Glu Lys Thr Gln Glu Ser Leu
195 200 205

<210> 167

<211> 81

<212> PRT

<213> Homo sapien

<400> 167

157

Ser Leu Leu Gly Arg Arg Arg Lys Leu His Leu Pro Asp Pro Asp Leu
1 5 10 15

Ala Ser Trp Gly Pro Gly Arg Ser Gly Ser Gly Gly Arg Trp Asp
20 25 30

Cys Met Cys Glu Cys Glu Cys Ala Cys Val Gly Glu Arg Glu Arg Arg
35 40 45

Phe Trp Glu Val Ala Lys Gly Leu Ala Ser Gly Ala Gly Gly Arg Asp
50 55 60

Ala Leu Trp Val Glu Ser Arg Val Lys Gly Ala Arg Arg Ser Gln Leu
65 70 75 80

Leu

<210> 168

<211> 154

<212> PRT

<213> Homo sapien

<400> 168

Val Ala Leu Val Pro Pro Gly Leu Leu Arg Thr Asp Pro Val Pro Glu
1 5 10 15

Glu Gly Glu Asp Val Ala Ala Thr Ile Ser Ala Thr Glu Thr Leu Ser
20 25 30

Glu Glu Glu Gln Glu Glu Leu Arg Arg Glu Leu Ala Lys Val Glu Glu
35 40 45

Glu Ile Gln Thr Leu Ser Gln Val Leu Ala Ala Lys Glu Lys His Leu
50 55 60

Ala Glu Ile Lys Arg Lys Leu Gly Ile Asn Ser Leu Gln Glu Leu Lys
65 70 75 80

Gln Asn Ile Ala Lys Gly Trp Gln Asp Val Thr Ala Thr Ser Ala Tyr
85 90 95

Lys Lys Thr Ser Glu Thr Leu Ser Gln Ala Gly Gln Lys Ala Ser Ala
100 105 110

Ala Phe Ser Ser Val Gly Ser Val Ile Thr Lys Lys Leu Glu Asp Val

158

115

120

125

Lys Asn Ser Pro Thr Phe Lys Ser Phe Glu Glu Lys Val Glu Asn Leu
130 135 140

Lys Ala Ser Arg Glu Met Asn Arg Val Phe
145 150

<210> 169
<211> 178
<212> PRT
<213> Homo sapien

<400> 169

Gly Gly Trp Val Thr Pro Gln Glu Ser Ala Pro Gly Arg Gly Arg Ala
1 5 10 15

Ala Pro Pro Arg Pro Thr Pro Leu Gly Val Gly Thr Ser Arg Glu Ser
20 25 30

Pro Ala Glu Ala Arg Arg Ser Ser Ala Arg Arg Gly Gly Arg Ser Glu
35 40 45

Pro Gly Arg Ala Ala Gly Gly Ala Ala Glu Asp Thr Arg Arg Arg
50 55 60

Ala Gly Asp Met Asp Arg Gly Glu Gln Gly Leu Leu Arg Thr Asp Pro
65 70 75 80

Val Pro Glu Glu Gly Glu Asp Val Ala Ala Thr Ile Ser Ala Thr Glu
85 90 95

Thr Leu Ser Glu Glu Glu Gln Glu Glu Leu Arg Arg Glu Leu Ala Lys
100 105 110

Val Glu Glu Glu Ile Gln Thr Leu Ser Gln Val Leu Ala Ala Lys Glu
115 120 125

Lys His Leu Ala Glu Ile Lys Arg Lys Leu Gly Ile Asn Ser Leu Gln
130 135 140

Glu Leu Lys Gln Asn Ile Ala Lys Gly Trp Gln Asp Val Thr Ala Thr
145 150 155 160

Ser Ala Arg Ser Lys Leu Leu Ala Ala Glu Thr Glu Leu Cys Leu
165 170 175

Leu Tyr

<210> 170
<211> 138
<212> PRT
<213> Homo sapien

<400> 170

Met Glu Lys Leu Ala Ala Ser Thr Glu Pro Gln Gly Pro Arg Pro Val
1 5 10 15

Leu Gly Arg Glu Ser Val Gln Val Pro Asp Asp Gln Asp Phe Arg Ser
20 25 30

Phe Arg Ser Glu Cys Glu Ala Glu Val Gly Trp Asn Leu Thr Tyr Ser
35 40 45

Arg Ala Gly Val Ser Val Trp Val Gln Ala Val Glu Met Asp Arg Thr
50 55 60

Leu His Lys Ile Lys Cys Arg Met Glu Cys Cys Asp Val Pro Ala Glu
65 70 75 80

Thr Leu Tyr Asp Val Leu His Asp Ile Glu Tyr Arg Lys Lys Trp Asp
85 90 95

Ser Asn Val Ile Glu Thr Phe Asp Ile Ala Arg Leu Thr Val Asn Ala
100 105 110

Asp Val Gly Tyr Tyr Ser Trp Arg Cys Pro Lys Pro Leu Arg Thr Tyr
115 120 125

Glu Val Pro Ser Ser Ile Arg Ser Cys Gln
130 135

<210> 171
<211> 187
<212> PRT
<213> Homo sapien

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> X=any amino acid

<220>
<221> MISC_FEATURE

160

<222> (174)..(174)
<223> X=any amino acid

<400> 171

Tyr Ile Gln Ser Cys Ser Val Pro His Arg Phe Ala Xaa Pro Arg Lys
1 5 10 15

Val Ala Ser Ala Ser Ala Ala Ser Thr Leu Ser Glu Pro Pro Arg
20 25 30

Arg Thr Gln Glu Ser Arg Thr Arg Thr Arg Ala Leu Gly Leu Pro Thr
35 40 45

Leu Pro Met Glu Lys Leu Ala Ala Ser Thr Glu Pro Gln Gly Pro Arg
50 55 60

Pro Val Leu Gly Arg Glu Ser Val Gln Val Pro Asp Asp Gln Asp Phe
65 70 75 80

Arg Ser Phe Arg Ser Glu Cys Glu Ala Glu Val Gly Trp Asn Leu Thr
85 90 95

Tyr Ser Arg Ala Gly Val Ser Val Trp Val Gln Ala Val Glu Met Asp
100 105 110

Arg Thr Leu His Lys Ile Lys Cys Arg Met Glu Cys Cys Asp Val Pro
115 120 125

Ala Glu Thr Leu Tyr Asp Val Leu His Asp Ile Glu Tyr Arg Lys Lys
130 135 140

Trp Asp Ser Asn Val Ile Glu Thr Phe Asp Ile Ala Arg Leu Thr Val
145 150 155 160

Asn Ala Asp Val Gly Tyr Tyr Ser Trp Ser Val Pro Ser Xaa Cys Glu
165 170 175

Pro Met Arg Tyr Arg Ala Arg Phe Asp His Val
180 185

<210> 172
<211> 201
<212> PRT
<213> Homo sapien

<400> 172

161

Met Glu Lys Leu Ala Ala Ser Thr Glu Pro Gln Gly Pro Arg Pro Val
1 5 10 15

Leu Gly Arg Glu Ser Val Gln Val Pro Asp Asp Gln Asp Phe Arg Ser
20 25 30

Phe Arg Ser Glu Cys Glu Ala Glu Val Gly Trp Asn Leu Thr Tyr Ser
35 40 45

Arg Ala Gly Val Ser Val Trp Val Gln Ala Val Glu Met Asp Arg Thr
50 55 60

Leu His Lys Ile Lys Cys Arg Met Glu Cys Cys Asp Val Pro Ala Glu
65 70 75 80

Thr Leu Tyr Asp Val Leu His Asp Ile Glu Tyr Arg Lys Lys Trp Asp
85 90 95

Ser Asn Val Ile Glu Thr Phe Asp Ile Ala Arg Leu Thr Val Asn Ala
100 105 110

Asp Val Gly Tyr Tyr Ser Trp Arg Cys Pro Lys Pro Leu Lys Asn Arg
115 120 125

Asp Val Ile Thr Leu Arg Ser Trp Leu Pro Met Gly Ala Asp Tyr Ile
130 135 140

Ile Met Asn Tyr Ser Val Lys His Pro Lys Tyr Pro Pro Arg Lys Asp
145 150 155 160

Leu Val Arg Ala Val Ser Ile Gln Thr Gly Tyr Leu Ile Gln Ser Thr
165 170 175

Gly Pro Lys Ser Cys Val Ile Thr Tyr Leu Gly Pro Gly Gly Pro Gln
180 185 190

Arg Leu Leu Thr Gln Val Gly Gly Glu
195 200

<210> 173
<211> 387
<212> PRT
<213> Homo sapien

<400> 173

Gln Pro Gly Lys Ser Arg Ala Ala Ala Ala Glu Pro Pro Ser Pro Arg
1 5 10 15

Ala Pro Ser Leu Ala Gly Arg Gly Ala Arg Gly Trp Gly Pro Gly Arg
20 25 30

Gly Arg Ala Ala Gly Pro Thr Ala Pro Pro Thr Arg Ala Pro Ala Arg
35 40 45

Pro Arg Val Ser Arg Ala Ala Ala Ala Ala Leu Ala Pro Arg Pro
50 55 60

Arg Arg Ala Pro Ala Glu Arg Arg Ala Lys Val Pro Gly Arg Trp Arg
65 70 75 80

Gln His Leu Gln Pro Arg Arg Cys Arg Ser Leu Pro Thr Leu Pro
85 90 95

Met Glu Lys Leu Ala Ala Ser Thr Glu Pro Gln Gly Pro Arg Pro Val
100 105 110

Leu Gly Arg Glu Ser Val Gln Val Pro Asp Asp Gln Asp Phe Arg Ser
115 120 125

Phe Arg Ser Glu Cys Glu Ala Glu Val Gly Trp Asn Leu Thr Tyr Ser
130 135 140

Arg Ala Gly Val Ser Val Trp Val Gln Ala Val Glu Met Asp Arg Thr
145 150 155 160

Leu His Lys Ile Lys Cys Arg Met Glu Cys Cys Asp Val Pro Ala Glu
165 170 175

Thr Leu Tyr Asp Val Leu His Asp Ile Glu Tyr Arg Lys Lys Trp Asp
180 185 190

Ser Asn Val Ile Glu Thr Phe Asp Ile Ala Arg Leu Thr Val Asn Ala
195 200 205

Asp Val Gly Tyr Tyr Ser Trp Arg Cys Pro Lys Pro Leu Lys Asn Arg
210 215 220

Asp Val Ile Thr Leu Arg Ser Trp Leu Pro Met Gly Ala Asp Tyr Ile
225 230 235 240

Ile Met Asn Tyr Ser Val Lys His Pro Lys Tyr Pro Pro Arg Lys Asp
245 250 255

163

Leu Val Arg Ala Val Ser Ile Gln Thr Gly Tyr Leu Ile Gln Ser Thr
260 265 270

Gly Pro Lys Ser Cys Val Ile Thr Tyr Leu Ala Gln Val Asp Pro Lys
275 280 285

Gly Ser Leu Pro Lys Trp Val Val Asn Lys Ser Ser Gln Phe Leu Ala
290 295 300

Pro Lys Ala Met Lys Lys Met Tyr Lys Ala Cys Leu Lys Tyr Pro Glu
305 310 315 320

Trp Lys Gln Lys His Leu Pro His Phe Lys Pro Trp Leu His Pro Glu
325 330 335

Gln Ser Pro Leu Pro Ser Leu Ala Leu Ser Glu Leu Ser Val Gln His
340 345 350

Ala Asp Ser Leu Glu Asn Ile Asp Glu Ser Ala Val Ala Glu Ser Arg
355 360 365

Glu Glu Arg Met Gly Gly Ala Gly Gly Glu Gly Ser Asp Asp Asp Thr
370 375 380

Ser Leu Thr
385

<210> 174
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<212> PRT
<213> Homo sapien

<400> 174

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Arg Ser Leu Pro Thr Leu Pro Met Glu Lys Leu Ala Ala Ser Thr Glu
20 25 30

Pro Gln Gly Pro Arg Pro Val Leu Gly Arg Glu Ser Val Gln Val Pro
35 40 45

Asp Asp Gln Asp Phe Arg Ser Phe Arg Ser Glu Cys Glu Ala Glu Val
50 55 60

Gly Trp Asn Leu Thr Tyr Ser Arg Ala Gly Val Ser Val Trp Val Gln

164

65

70

75

80

Ala Val Glu Met Asp Arg Thr Leu His Lys Ile Lys Cys Arg Met Glu
85 90 95

Cys Cys Asp Val Pro Ala Glu Thr Leu Tyr Asp Val Leu His Asp Ile
100 105 110

Glu Tyr Arg Lys Lys Trp Asp Ser Asn Val Ile Glu Thr Phe Asp Ile
115 120 125

Ala Arg Leu Thr Val Asn Ala Asp Val Gly Tyr Tyr Ser Trp Arg Cys
130 135 140

Pro Lys Pro Leu Lys Asn Arg Asp Val Ile Thr Leu Arg Ser Trp Leu
145 150 155 160

Pro Met Gly Ala Asp Tyr Ile Ile Met Asn Tyr Ser Val Lys His Pro
165 170 175

Lys Tyr Pro Pro Arg Lys Asp Leu Val Arg Ala Val Ser Ile Gln Thr
180 185 190

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210 215 220

<210> 175
<211> 314
<212> PRT
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<400> 175

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Pro Gln Gly Pro Arg Pro Val Leu Gly Arg Glu Ser Val Gln Val Pro
35 40 45

Asp Asp Gln Asp Phe Arg Ser Phe Arg Ser Glu Cys Glu Ala Glu Val
50 55 60

165

Gly Trp Asn Leu Thr Tyr Ser Arg Ala Gly Val Ser Val Trp Val Gln
65 70 75 80

Ala Val Glu Met Asp Arg Thr Leu His Lys Ile Lys Cys Arg Met Glu
85 90 95

Cys Cys Asp Val Pro Ala Glu Thr Leu Tyr Asp Val Leu His Asp Ile
100 105 110

Glu Tyr Arg Lys Lys Trp Asp Ser Asn Val Ile Glu Thr Phe Asp Ile
115 120 125

Ala Arg Leu Thr Val Asn Ala Asp Val Gly Tyr Tyr Ser Trp Arg Cys
130 135 140

Pro Lys Pro Leu Lys Asn Arg Asp Val Ile Thr Leu Arg Ser Trp Leu
145 150 155 160

Pro Met Gly Ala Asp Tyr Ile Ile Met Asn Tyr Ser Val Lys His Pro
165 170 175

Lys Tyr Pro Pro Arg Lys Asp Leu Val Arg Ala Val Ser Ile Gln Thr
180 185 190

Gly Tyr Leu Ile Gln Ser Thr Gly Pro Lys Ser Cys Val Ile Thr Tyr
195 200 205

Leu Ala Gln Val Asp Pro Lys Gly Ser Leu Pro Lys Trp Val Val Asn
210 215 220

Lys Ser Ser Gln Phe Leu Ala Pro Lys Ala Met Lys Lys Met Tyr Lys
225 230 235 240

Ala Cys Leu Lys Tyr Pro Glu Trp Lys Gln Lys His Leu Pro His Phe
245 250 255

Lys Pro Trp Leu His Pro Glu Gln Ser Pro Leu Pro Ser Leu Ala Leu
260 265 270

Ser Glu Leu Ser Val Gln His Ala Asp Ser Leu Glu Asn Ile Asp Glu
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Ser Ala Val Ala Glu Ser Arg Glu Glu Arg Met Gly Gly Ala Gly Gly
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166

Glu Gly Ser Asp Asp Asp Thr Ser Leu Thr
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<400> 176

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20 25 30

Phe Arg Ser Glu Cys Glu Ala Glu Val Gly Trp Asn Leu Thr Tyr Ser
35 40 45

Arg Ala Gly Val Ser Val Trp Val Gln Ala Val Glu Met Asp Arg Thr
50 55 60

Leu His Lys Ile Lys Cys Arg Met Glu Cys Cys Asp Val Pro Ala Glu
65 70 75 80

Thr Leu Tyr Asp Val Leu His Asp Ile Glu Tyr Arg Lys Lys Trp Asp
85 90 95

Ser Asn Val Ile Glu Thr Phe Asp Ile Ala Arg Leu Thr Val Asn Ala
100 105 110

Asp Val Gly Tyr Tyr Ser Trp Arg Cys Pro Lys Pro Leu Lys Asn Arg
115 120 125

Asp Val Ile Thr Leu Arg Ser Trp Leu Pro Met Gly Ala Asp Tyr Ile
130 135 140

Ile Met Asn Tyr Ser Val Lys His Pro Lys Tyr Pro Pro Arg Lys Asp
145 150 155 160

Leu Val Arg Ala Val Ser Ile Gln Thr Gly Tyr Leu Ile Gln Ser Thr
165 170 175

Gly Pro Lys Ser Cys Val Ile Thr Tyr Leu Gly Pro Gly Gly Pro Gln
180 185 190

Ser Ser Leu Pro Lys Trp Val Val Arg Leu Leu Pro Arg Cys Pro Ala
195 200 205

Pro Arg Met Arg Leu Leu Val Leu Leu Trp Gly Cys Leu Leu Leu Pro
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Gly Tyr Glu Ala Leu Glu Gly Pro Glu Glu Ile Ser Gly Phe Glu Gly
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245 250 255

Arg Lys Tyr Trp Cys Arg Lys Gly Gly Ile Leu Phe Ser Arg Cys Ser
260 265 270

Gly Thr Ile Tyr Ala Glu Glu Gly Gln Glu Thr Met Lys Gly Arg
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Val Ser Ile Arg Asp Ser Arg Gln Glu Leu Ser Leu Ile Val Thr Leu
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Thr Arg Thr Arg Ala Leu Gly Leu Pro Thr Leu Pro Met Glu Lys Leu
50 55 60

168

Ala Ala Ser Thr Glu Pro Gln Gly Pro Arg Pro Val Leu Gly Arg Glu
65 70 75 80

Ser Val Gln Val Pro Asp Asp Gln Asp Phe Arg Ser Phe Arg Ser Glu
85 90 95

Cys Glu Ala Glu Val Gly Trp Asn Leu Thr Tyr Ser Arg Ala Gly Val
100 105 110

Ser Val Trp Val Gln Ala Val Glu Met Asp Arg Thr Leu His Lys Ile
115 120 125

Lys Cys Arg Met Glu Cys Cys Asp Val Pro Ala Glu Thr Leu Tyr Asp
130 135 140

Val Leu His Asp Ile Glu Tyr Arg Lys Lys Trp Asp Ser Asn Val Ile
145 150 155 160

Glu Thr Phe Asp Ile Ala Arg Leu Thr Val Asn Ala Asp Val Gly Tyr
165 170 175

Tyr Ser Trp Arg Cys Pro Lys Pro Leu Lys Asn Arg Asp Val Ile Thr
180 185 190

Leu Arg Ser Trp Leu Pro Met Gly Ala Asp Tyr Ile Ile Met Asn Tyr
195 200 205

Ser Val Lys His Pro Lys Tyr Pro Pro Arg Lys Asp Leu Val Arg Ala
210 215 220

Val Ser Ile Gln Thr Gly Tyr Leu Ile Gln Ser Thr Gly Pro Lys Ser
225 230 235 240

Cys Val Ile Thr Tyr Leu Ala Gln Val Asp Pro Lys Ala Pro Tyr Pro
245 250 255

Ser Gly Trp Cys Val Cys Ser His Gly Val Gln Arg Pro Glu Cys Gly
260 265 270

Phe Trp Ser Cys Tyr Gly Val Ala Cys Cys Ser Gln Val Met Lys Pro
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Trp Arg Ala Gln Arg Lys Ser Ala Gly Ser Lys Gly Thr Leu Cys Pro
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Cys Ser Ala Pro Thr Gly Lys Ser

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<400> 178

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Asn Lys Ser Tyr Ser Ser Leu Gly Asn Lys Ser Tyr Ser Ser Leu Gly
35 40 45

Asn Glu Gly Pro Arg Ala Ala Ser Ser Pro Thr Trp Ala Gln Val Asp
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Pro Lys Gly Ser Leu Pro Lys Trp Val Val Asn Lys Ser Ser Gln Phe
65 70 75 80

Leu Ala Pro Lys Ala Met Lys Lys Met Tyr Lys Ala Cys Leu Lys Tyr
85 90 95

Pro Glu Trp Lys Gln Lys His Leu Pro His Phe Lys Pro Trp Leu His
100 105 110

Pro Glu Gln Ser Pro Leu Pro Ser Leu Ala Leu Ser Glu Leu Ser Val
115 120 125

Gln His Ala Asp Ser Leu Glu Asn Ile Asp Glu Ser Ala Val Ala Glu
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Asp Thr Ser Leu Thr
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<210> 179
<211> 155
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<400> 179

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20 25 30

Arg Ala Thr Pro Ala Trp Ala Ile Arg Pro Lys Ser Cys Val Ile Thr
35 40 45

Tyr Leu Ala Gln Val Asp Pro Lys Gly Ser Leu Pro Lys Trp Val Val
50 55 60

Asn Lys Ser Ser Gln Phe Leu Ala Pro Lys Ala Met Lys Lys Met Tyr
65 70 75 80

Lys Ala Cys Leu Lys Tyr Pro Glu Trp Lys Gln Lys His Leu Pro His
85 90 95

Phe Lys Pro Trp Leu His Pro Glu Gln Ser Pro Leu Pro Ser Leu Ala
100 105 110

Leu Ser Glu Leu Ser Val Gln His Ala Asp Ser Leu Glu Asn Ile Asp
115 120 125

Glu Ser Ala Val Ala Glu Ser Arg Glu Glu Arg Met Gly Gly Ala Gly
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<400> 181

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19

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<211> 29
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<213> Artificial sequence

<220>
<223> Synthetic

<400> 182
tttgttgtta atgtaattag agacaccag

29

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International Bureau



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24 June 2004 (24.06.2004)

PCT

(10) International Publication Number
WO 2004/053075 A3

(51) International Patent Classification⁷: C12Q 1/68, C12P 21/02, C12N 15/00, 15/12, 15/11, A61K 31/7088, 31/711

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(71) Applicant (for all designated States except US): **DI-ADEXUS, INC.** [US/US]; 343 Oyster Point Boulevard, South San Francisco, CA 94080 (US).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MACINA, Roberto, A.** [AR/US]; 4118 Crescendo Avenue, San Jose, CA 95136 (US). **TURNER, Leah, R.** [US/US]; 939 Rosette Court, Sunnyvale, CA 94086 (US). **SUN, Yongming** [CN/US]; 551 Shoal Circle, Redwood City, CA 94065 (US).

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4 November 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(74) Agents: **LICATA, Jane, Massey et al.**; Licata & Tyrrel P.C., 66 E. Main Street, Marlton, NJ 08053 (US).

WO 2004/053075 A3

(54) Title: COMPOSITIONS, SPLICE VARIANTS AND METHODS RELATING TO BREAST SPECIFIC GENES AND PROTEINS

(57) Abstract: The present invention relates to newly identified nucleic acid molecules and polypeptides present in normal and neoplastic breast cells, including fragments, variants and derivatives of the nucleic acids and polypeptides. The present invention also relates to antibodies to the polypeptides of the invention, as well as agonists and antagonists of the polypeptides of the invention. The invention also relates to compositions containing the nucleic acid molecules, polypeptides, antibodies, agonists and antagonists of the invention and methods for the use of these compositions. These uses include identifying, diagnosing, monitoring, staging, imaging and treating breast cancer and non-cancerous disease states in breast, identifying breast tissue, monitoring and identifying and/or designing agonists and antagonists of polypeptides of the invention. The uses also include gene therapy, production of transgenic animals and cells, and production of engineered breast tissue for treatment and research.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/38739

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; C12P 21/02; C12N 15/00, 15/12, 15/11; A61K 31/7088, 31/711
 US CL : 536/23.1, 23.5; 435/6, 320.1, 325, 252.3, 69.1; 514/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.5; 435/6, 320.1, 325, 252.3, 69.1; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 Compugen, SEQ ID NO: 73

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GU, J.Z. et al, The human B22 subunit of the NADH-ubiquinone oxidoreductase maps to the region of chromosome 8 involved in branchio-oto-renal syndrome, Genomics, 1996, Vol. 36, No. 1, pages 6-10, see especially page 8, Figure 1.	1-3, 5, 6, 8, and 9
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Y		4 and 10

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

18 August 2004 (18.08.2004)

Date of mailing of the international search report

14 SEP 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
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 Alexandria, Virginia 22313-1450

Faxsimile No. (703)305-3230

Authorized officer

James Martinell

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/38739

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-10 and 15-17.

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-10 and 15-17, drawn to nucleic acids, nucleic acid molecular hybridization assays, vectors, host cells, methods for producing polypeptides, kits, vaccines, and methods of treatment using nucleic acids.

Group II, claim(s) 1, 12, and 16-18, drawn to polypeptides, kits, vaccines, and methods of treatment using polypeptides.

Group III, claim(s) 13-15, drawn to antibodies and protein binding assays.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The nucleic acids, vectors, host cells, nucleic acid containing kits, and nucleic acid vaccines of Group I are materially different from the polypeptides, kits containing polypeptide, and polypeptide vaccines of Group II, and the antibodies of Group III. The methods of Group I may be practiced without the products or compositions of Group II or the antibodies of Group III. The methods of Groups I-III may be practiced independently of one another. The polypeptides and vaccines of Group II are materially different from the antibodies of Group III and are not needed to practice the methods of Group III.

Each of the Groups mentions a matter which additional Group for search. Any additional SEQ ID NO(s) of payment of additional search fees for additional Groups to be searched otherwise.

rate and unrelated nucleic acids and/or polypeptides. No need to select for search one SEQ ID NO within the Group(s) requires one additional search fee per SEQ ID NO. In the absence of Group I will be searched. Should applicant pay fee(s) for the selected Group will be searched unless applicant directs otherwise.